An Investigation of the Acute and Chronic Effects of Ketamine on Cognition

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Abstract

The work presented in this thesis aimed to investigate the consequences and causes of ketamine abuse and compare them with the acute effects of the drug. Seven experimental chapters report the findings of a total of 9 studies: 5 with ketamine users, 3 administering ketamine to healthy volunteers and 1 with psychosis-prone individuals. Acute studies with volunteers demonstrated ketamine-induced impairments to item recognition, source memory, controlled semantic processing, working memory and procedural learning. There was also a suggestion of a disruption in self-monitoring but perceptual priming and executive functioning were largely preserved. Ketamine was subjectively reinforcing in healthy volunteers. Suggested chronic effects of ketamine in drug users included deficits in source memory and controlled semantic processing indicative of a degraded semantic store. Following substantial reduction in ketamine use, semantic function appeared to recover whilst episodic and attentional impairments appeared persistent. Overall, this thesis suggested that ketamine, both acutely and chronically, produces selective cognitive impairments, particularly to those functions that require integration of contextual information. The implications of this thesis are drawn out for an acute versus 'chronic' model of psychosis. Chronic deficits in ketamine users may reflect neurological changes associated with repeated NMDA-receptor antagonism and hence may be more similar to changes observed in the later stages of schizophrenia, whereas acute ketamine may better model the acute phase. Persisting cognitive impairments are of concern in light of the burgeoning population of ketamine users.

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Morgan CJA, Monaghan L, Curran HV (2004c) Beyond the K-hole: A 3-year longitudinal investigation of the cognitive and subjective effects of ketamine, in recreational users who have substantially reduced their use of the drug. Addiction 99:1450-61.

Morgan CJA, Ricelli M, Maitland CH, Curran HV (2004d) Long-term effects of ketamine: evidence for a persisting impairment of source memory in recreational users. Drug and Alcohol Dependence 75: 301-308

Morgan, CJA, Rossell SL, Peppr, F, Smart, J, Blackburn, J, Brandner, B, Curran HV (submitted) Semantic priming after ketamine acutely in healthy volunteers and following chronic self-administration in substance users.

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Across all graphs T-bars represent the standard error of the mean (SEM).

Selected Abbreviations and Acronyms

NMDA-R	N-methy-D-aspartate receptor
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolepropanoic acid
Glu	Glutamate
DA	Dopamine
GABA	γ-aminobutyric acid
ACh	Acetylcholine
PCP	Phencyclidine
MDMA	±3,4 –methylenedioxymethamphetamine
LTP	Long term potentiation
FA	False Alarm
HT	Hit
RT	Reaction Time
PE	Perseverative Error
SOA	Stimulus onset asynchrony
MePI	Mepulse Inhibition
PPI	Prepulse inhibition
SD	Standard Deviation
SSQ	Schizotypal Symptomatology Questionnaire
ADDS	Adapted Dissociative States Scale
MRS	Mood Rating Scale
VAS	Visual Analogue Scale
SES	Subjective Effects Scale
PFC	Prefrontal Cortex
DLPFC	Dorsolateral prefrontal cortex
fMRI	Functional magnetic resonance imaging
PET	Positron Emission Tomography

Chapter 1: Introduction

"Words are, of course, the most powerful drug used by mankind"

Rudyard Kipling

This chapter is structured in two parts. Following a brief historical consideration of the use and abuse of ketamine and related compounds, a summary is presented of their chemical mechanism and neuropharmacology. This background section then leads on to a review of the literature on the cognitive and psychotomimetic properties of N-methyl-D-aspartate receptor antagonists.

1.1. History of the use of ketamine and related compounds in anaesthesia

Ketamine is a member of a class of compounds known as arylcyclohexylamines, with others being phencyclidine (PCP) and MK-801. PCP was the first compound of this group to be synthesised. Originally, it was designed for use as an anaesthetic and was given to humans in the late 1950s (Greifenstein et al., 1958). Whilst PCP did have profound analgesic and anaesthetic effects, in approximately 50% of patients the drug also induced severe reactions characterised by agitation, paranoia, depersonalisation, concreteness of thought, bizarre behaviour and hallucinations (Johnstone et al., 1958) which persisted for up to 6 hours and could produce a psychotic phase lasting several weeks (Aniline & Pitts, 1982). These undesirable post-operative psychotomimetic effects, combined with its duration of action, led to the drug being withdrawn from anaesthetic use in humans (Grinspoon & Bakalar, 1997). It did however continue to be used as a tranquilliser for animals marketed under the name Sernylan.

Impressed by the analgesic and anaesthetic properties of PCP, Parke Davis developed a congener of PCP in 1962 for use in human anaesthesia: 2-orthochlorophenyl, 2-methylamino cyclohexanone hydrochloride or CI 581. Later called ketamine hydrochloride, this compound was purported to offer the same benefits as PCP but with fewer psychotomimetic side-effects. Ketamine was described as producing:

> " ... *profound analgesia and short lasting anaesthesia...Respiratory depression is transient and not a serious problem... Many protective reflexes such as laryngeal, pharyngeal, eyelid and corneal are present during the patients' unresponsiveness. No liver, kidney, or blood abnormalities or venous irritation were noted in the subjects tested...* "
>
> Domino, Chodoff & Corssen, (1965, pp.279)

The unique cataleptic-like state associated with ketamine, and indeed other arylcyclohexamines, where patients were fully awake but "..not there.." led Edward Domino (1965) to coin the term 'dissociative anaesthetic' to describe this class of drugs. However, with increasing experience of ketamine, clinicians noticed complications associated with the use of the drug similar to, although more transient than, those observed with PCP. Post-operatively patients experienced confusional states, vivid dreaming and hallucinations (Siegel, 1978). These side effects limited the routine use of ketamine in anaesthesia (Goodman & Gilman, 2001). Nevertheless, the unique effects of ketamine mean that it continues to be used as an anaesthetic within veterinary and paediatric anaesthesia and for anaesthetising patients at risk of hypotension and bronchiospasm. The highly effective analgesia is also considered useful for treating burns victims and in emergency field work. Indeed, the drug was the most popular anaesthetic used in the Vietnam War (Siegel, 1978). Ketamine is also used in intensive treatment units and palliative care for its profound analgesic effects. More recently ketamine has enjoyed some success in the treatment of chronic pain patients (Enarson et al., 1999) although it is still not licensed for this use (Joint Formulary Committee, 2005).

1.2 History the abuse of ketamine and PCP by recreational users

Precisely the effects that limited the clinical use of ketamine and PCP were those that made the drug popular with recreational users. Reports first spread of PCP abuse in the late sixties where it appeared on the streets under a variety of names; 'angel dust', 'hog' and 'super weed' (Feldman et al., 1997). In the early seventies it was placed on the schedule of controlled drugs in the United States. Use of PCP rose throughout the 1970s but has steadily declined since 1979 (Johnston et al., 1987). PCP also became

controlled under the Misuse of Drugs Act (1971) as a Class A drug in the U.K, although is nowadays very rarely found in this country (DrugScope, 2001).

Street use of ketamine was first noted in 1971 in the U.S. (Siegel, 1978) where it was primarily sold in solution but by 1974 there were reports of its sale in powder and tablet form. By the mid 1970's the recreational use of ketamine had spread to countries such as England, Sweden and Russia (Kelly, 1999). Despite worldwide reports of use of the drug, at this stage the numbers of recreational users were still relatively small.

The last two decades have seen a rapid increase in the use of ketamine with the advent of dance music culture. Ketamine first appeared on the 'rave' scene as a contaminant in ±3,4-methylenedioxymethamphetamine (MDMA, 'ecstasy') tablets (Dalgarno & Shewan, 1996) but then became available in its pure form where it is referred to as 'Special K', 'K' , 'K50', 'Gold-top', 'Vitamin K' and 'Super K' (Curran & Morgan, 2000). Reports of increasing recreational ketamine use appeared in the medical literature (e.g. Dalgarno & Shewan, 1996) and in the popular media (McDermott, 1992) in the late 1990's. A survey of London night-clubs found that 40% of the 200 respondents had experimented with ketamine and intended to use it the same evening (Release, 1997; McDermott, 1992). A more recent survey suggested there may be approximately 90 000 regular, and 500 000 occasional ketamine users in the UK (Independent Drug Monitoring Unit: IDMU, 2005). The increase in ketamine abuse in the U.S was such that ketamine became a Schedule III drug at the federal level. (F.D.A., 1999). In the U.K. ketamine is not controlled under the Misuse of Drugs Act (1971). It is controlled under the Medicines Act (1968) however this status is currently under review (Advisory Council on the Misuse of Drugs - ACMD 2004) .

Debate over the long-term effects of ketamine has raged since the very beginning of its recreational use when a ketamine user, wrote of the drug:

"*...If captains of industry, leaders of nations could partake of this love medicine then the whole planet might be converted into the Garden of Eden ...* "

Marcia Moore, Journeys into the Bright World (Moore & Altounian, 1978)

Her husband, Howard Altounian, an anaesthetist, expressed a different view:

"*Marcia became addicted to ketamine and committed suicide (January 14th, 1979). Ketamine is dangerous. Its use should not be encouraged...*"

Howard Altounian (1998) c.f. Jansen (2001)

For the growing population of recreational users there is a clear need to investigate the dependence forming potential of ketamine and to characterise the side effects associated with long term use of this drug.

1.3 Basic pharmacology of ketamine, PCP and dizocilipine

The chemical structure of ketamine is shown in Figure 1.1. Ketamine, PCP and dizocilipine are lipid soluble molecules that readily cross the blood-brain barrier following peripheral administration. Preclinical work has demonstrated that ketamine and PCP are stored in adipose tissue and then slowly released back into the plasma compartment (Martin & Lodge, 1985). The alpha phase of ketamine distribution lasts about 45 minutes, with a half-life of 10 to 15 minutes. This first phase corresponds clinically to the anaesthetic effect of the drug. When administered intravenously for anaesthesia, a sensation of dissociation occurs within 15 seconds and anaesthesia occurs within 30 seconds (in 3-4 minutes for intra-muscular (IM) route). The anaesthetic effects are terminated by a combination of redistribution and hepatic biotransformation to an active metabolite, norketamine (Goodman & Gilman, 2001). Norketamine has itself been suggested to have some psychotomimetic effects (Lindefors et al., 1997). The terminal half life of ketamine is about 2-3 hours.

Ketamine and PCP are available in solutions for injection for anaesthetic use (either IM or IV). Recreational ketamine and PCP users use a variety of routes of administration. PCP can be injected, taken intranasally or orally, or smoked. Ketamine is generally self-administered intranasally but some users inject the drug or take it orally. After

intranasal administration of ketamine onset of effects is between 5 - 15 min, duration approximately 45 - 60 min and after about 2 - 4 hours users are back to baseline (Jansen, 2000). Nasal doses are highly nonlinear compared with oral and IM doses however Erowid (2002), an internet based drug user resource, suggests that a dose of 100mg - 200mg is enough for users to achieve what is referred to as "The K-hole". This is a highly dissociated catatonic state where the user experiences dramatic hallucinations and minimal self-awareness.

1.4 The chemical mechanism of the arylcyclohexylamines

Early studies of the pharmacology of PCP and ketamine suggested a variety of candidates for the neurochemical induction of their psychotomimetic and cognitive effects. Initial suggestions regarding the mechanism of PCP-induced effects included: increased dopamine release and blockade of dopamine reuptake; elevated 5-HT levels; potentiation of acetylcholine release; and various effects at α-noradrenergic receptors, sigma receptors and Gamma-aminobutyric acid (GABA) receptors (Domino et al., 1965). But whilst PCP was found to interact with these targets, the majority of these interactions occurred at concentrations unlikely to be reached in clinical situations. Zukin and Zukin (1979) reasoned that the PCP receptor site within the N-methyl-D-aspartate receptor complex (NMDA-R) at which the neurotransmitter glutamate functions - a site with submicromolar affinity for PCP, ketamine and MK-801 - was the best candidate receptor in mediating the behavioural effects of these compounds.

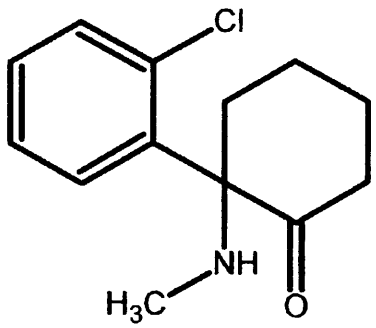


Figure 1.1: Ketamine molecule

1.5 Glutamate, the NMDA –receptor complex and Long–Term Potentiation

Glutamate is an amino acid that can be readily synthesised in the brain and thus is not required in the diet. The excitatory properties of glutamate were first described by Hayashi (1954) and but it was not until the last two decades (Watkins & Evams, 1981) that glutamate was recognised as the major excitatory neurotransmitter in the brain (Javitt & Zukin, 1991) . The glutamate system is composed of widely spread projections to most brain regions. Glutamate is implicated in both the rapid transfer of information between cortical and sub-cortical structures and in longer term changes related to the adaptation of the central nervous system (CNS) over time (Feldman et al. 1996). The NMDA-R is one type of glutamate receptor, others include other iontropic receptors e.g. α-amino-3-hydroxy-5-methyl-4-isoxazolepropanoic acid (AMPA) and kainate receptors and metabotropic glutamate receptors. The functioning of the NMDA-R has been extensively investigated leading to a thorough understanding of the mechanism by which it operates.

The NMDA-R controls a calcium channel (Javitt & Zukin, 1991) and the receptor functioning is dependent upon the potential of the neuronal membrane. At the physiological resting membrane potential, magnesium ions (Mg^{2+}) effectively block ion fluxes through the NMDA-receptor gated ion channel. When the membrane is depolarised, the Mg^{2+} block is displaced and the binding of glutamate and glycine to their sites on the NMDA-R allows the channel to open and calcium ions (Ca^{2+}) to enter the channel, the calcium is excitatory and the potential passes between the presynaptic and post-synaptic cells. However, if there is prolonged and excessive influx of Ca^{2+} into the neuron toxicity can occur. This is a simplified explanation of a phenomena known as excitotoxicity which is the putative mechanism underlying neuronal degeneration arising from cerebral ischaemia (disruption of blood flow to the brain), hypoxia (reduction of oxygen blood flow) (Olney et al., 1989), epilepsy (Choi, 1990) and other neurological disorders.

Another important mechanism which the NMDA-R is proposed to mediate is long-term potentiation (LTP). LTP is the putative mechanism of neuronal learning and was first conceived by Donald Hebb in 1949 (Hebb, 1949). He proposed that learning occurs when the strength of synaptic connections rises among neurons that are active at the

same time i.e. neurons that fire together, wire together. Briefly, the mechanism of LTP is proposed to begin with glutamatergic signalling at AMPA and kainate receptors, reflecting pre-synaptic depolarisation of a certain critical frequency. Prolonged activation then facilitates functioning of the post-synaptic NMDA-R (Kandel, 1991). NMDA-R activation raises intracellular Ca^{2+} and has downstream effects on calcium dependent protein kinases leading to a cascade of events altering cellular function and gene transcription (See Figure 1.2). The postsynaptic cell also releases retrograde signalling molecules (possibly nitrous oxide) effecting intracellular machinery of the pre-synaptic cell (Thomas, 1995). In this way both the capacity of the pre-synaptic cell to release glutamate and the post-synaptic cell to detect it are altered (See Figure 1.2). More recently other forms of synaptic plasticity involving NMDA-R and non-NMDA glutamate receptors have been documented including long-term depression (LTD) and short-term potentiation (STP) (Thomas, 1995). Much of the evidence for the role of the NMDA-R in LTP and other forms of synaptic plasticity comes from pre-clinical work with NMDA-R antagonists which will be reviewed later in this chapter.

1.6. Effects on other neurotransmitter systems

As discussed above, the behavioural effects of the aryclcylohexamines are thought to be largely mediated by glutamatergic neurotransmission at the NMDA-receptor. However, the arycyclohexamines are also recognised as having downstream actions on other neurotransmitters systems in the brain.

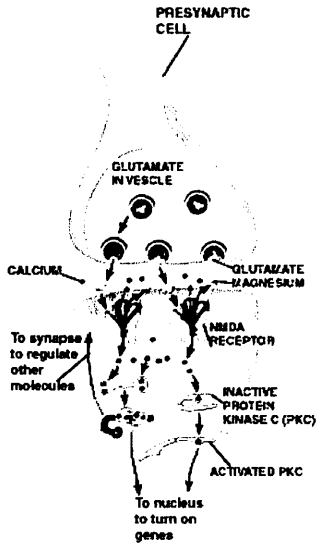


Figure 1.2: The NMDA-receptor complex and LTP

There has been considerable debate about the dopaminergic effects of ketamine and PCP. Low concentrations have been shown to antagonise NMDA-evoked DA release in the striatum (Moghaddam et al., 1997) . However, many of the behavioural effects of ketamine and PCP resemble those of a DA agonist (e.g. psychotomimetic properties and stereotypy in rats). At sub-anaesthetic doses NMDA-receptor antagonists increase extracellular DA concentrations in the rat pre-frontal cortex (Lindefors et al., 1997; Moghaddam et al., 1997). This increase in DA is associated with poorer performance on a working memory task (Verma & Moghaddam, 1997). Some positron emission tomography (PET) studies have demonstrated that ketamine stimulates the release of dopamine from striatal terminals (Smith et al., 1998) although more recent studies cast some doubt over these findings (Aalto et al., 2002; Kegeles et al., 2002).

PCP and ketamine have also been shown to inhibit NMDA-stimulated ACh release from rat cerebral cortical and striatal slices at very low concentrations (nanomolar to micromolar) (Kegeles et al. 2002; Lodge & Johnston, 1985). However, more recent animal studies also suggest an increase in cortical acetylcholine release with administration of acute and repeated doses of ketamine (Nelson et al., 2002). MK-801 and PCP have been shown to inhibit NMDA-induced cortical GABA release (Drejer & Honore, 1987). Ketamine also interacts with μ-opiod receptors and with the non-opiod σ receptor site, although the affinities of the drug for these receptors is at least one order of magnitude lower than for the PCP site (Oye et al., 1992). Effects of these drugs on other neurotransmitter systems will be given further consideration in Section 1.3.7 when interactive effects of the arylcyclohexamines and other drugs will be discussed.

1.7 PET and BOLD fMRI studies with ketamine and PCP

Given that the main behavioural effects of ketamine and related compounds have been attributed to NMDA-R antagonism, the areas of brain activation associated with the administration of NMDA-R antagonists might be hypothesised to those with a high concentration of NMDA-Rs. Although NMDA-Rs are located throughout the mammalian brain, the highest densities are in the cerebral cortex, the limbic system and striatum (Monaghan et al., 1985). Preliminary work with rodents using

autoradiographic techniques supported the view that NMDA-R antagonist-mediated brain activation occurs where NMDA-R populations are located. Studies demonstrated increased activation in cortical and limbic regions after ketamine and PCP administration (Crosby et al., 1982; Meibach et al., 1979). Further animal research has used ^{14}C-2-deoxyglucose (2DG) techniques and immunocyctochemical staining for Fos-like proteins (Fos-Li) to examine the effects of ketamine on brain metabolic activity (Duncan et al., 1998). At a sub-anaesthetic dose of 35 mg kg $^{-1}$ ketamine increased metabolic activity in limbic and cortical regions including the medial prefrontal, ventrolateral orbital, cingulate and retrosplenial cortices. Ketamine also increased metabolism in areas of the hippocampal formation and in select thalamic nuclei and the basolateral amygdala. Human studies using positron emission tomography (PET) methodology have shown marked increases in frontal cortex activity after ketamine administration (Vollenweider et al., 1997) in addition to increased activity in the anterior cingulate cortex. The frontal cortex is also more stimulated by ketamine than the occipital cortex, despite nearly equal NMDA-R densities (Breier et al., 1997) and it has been suggested that reduction of the inhibitory influence of GABAergic activity may result in some of the hyperfrontality observed following ketamine administration. In a further study using FDG-PET, ketamine was associated with an increase in activation in the prefrontal cortex but no other region (Hartvig et al., 1995).

Blood oxygen level dependent (BOLD) changes observed with functional magnetic resonance imaging (fMRI) has provided a new perspective on brain activity associated with ketamine. Abel et al.(2003b) suggested that ketamine's effects are not either a global increase or decrease in activation but represent increases in activity relative to task specific demands, and demonstrated these effects on a gender discrimination task. This assertion has been supported by subsequent work (Honey et al., 2005; Honey et al., 2004). These results will be discussed further in the section concerning acute effects of ketamine in humans (Section 1.9).

Studies in schizophrenic populations have also examined changes in brain haemodynamics following ketamine. Ketamine induced an increase in blood flow to the anterior cingulate and a decrease in blood flow to the hippocampus and primary

visual cortex in five schizophrenic patients examined with [^{15}O]H_2O PET (Lahti et al., 1995a) . Medoff et al. (2001) used a similar PET technique and found that a low dose of ketamine reduced blood flow in the hippocampus of a schizophrenic group but did not affect blood flow in healthy volunteers. This may be due to underlying differences in NMDA-R antagonist sensitivity in normal and schizophrenic volunteers (Medoff et al., 2001). Two studies have examined the effect of chronic NMDA-R antagonist administration in humans. They both found a reduction in frontal blood flow in drug-free PCP users compared to poly-drug taking controls (Hertzman et al., 2002) and healthy volunteers (Wu et al., 1991).

1.8 Summary

The principal mode of action of ketamine, PCP and MK-801 is at the PCP-receptor site of the NMDA-R complex. The magnitude of the behavioural effects of each drug is thought to be associated with their relative affinity for the NMDA-R; of which ketamine has the lowest affinity. These drugs are also reported to have effects at other receptors (e.g. DA, GABA and opiate receptors). The degree to which these effects on different systems may be responsible for some of the cognitive and psychotomimetic effects of ketamine and related compounds is not yet clear. Some research has begun to investigate this and is described in Section 1.9.7.

Hyperfrontality after ketamine has been found in two PET studies investigating brain activation changes along with increased activation of the anterior cingulate cortex. Task dependent increases in activation have been found in similar areas on fMRI studies. Acute ketamine challenge in schizophrenic patients has been associated with decreased activation of the hippocampus and increased anterior cingulate function but not increased frontal functioning. This may reflect some underlying differences in sensitivity to NMDA-R antagonists as a result of endogenous psychosis or neurodegenerative changes.

LITERATURE REVIEW

From the background given above it is apparent that ketamine and other NMDA-receptor antagonists provide unique tools to investigate the link between human, animal and neuronal models of learning and memory. The drug also induces a state resembling both the positive and negative symptoms of schizophrenia, thus the psychotomimetic properties of ketamine have been investigated to gain insight into the pathophysiology of schizophrenia. In addition, ketamine is increasingly being abused by recreational drug users in dance venues and 'raves' and some research has examined the effects of chronic abuse of this drug. It is in these three contexts that literature surrounding NMDA-receptor antagonists will be discussed in this review.

Part I: Acute and sub-acute studies of the cognitive effects of NMDA-R antagonists will outline studies of the acute and sub-acute effects of NMDA-R antagonists discussed in the framework of Tulving's (1985) memory systems model. This section will mention pre-clinical research but focus mainly on the effects of NMDA-R antagonists in humans.

Part II: Acute and sub-acute studies of the psychotomimetic effects of NMDA-R antagonists will provide a general background to schizophrenia and cognitive dysfunction associated with it. Then studies of the acute and sub-acute psychotomimetic effects of NMDA-R antagonists in animals and humans will be reviewed. Symptom exacerbation studies will also be reviewed in addition to studies looking at the interactive effects of ketamine and antipsychotic and sedative compounds.

Part III: Chronic Effects of NMDA-R antagonists will examine the literature concerning the chronic effects of NMDA-receptor antagonists. Preclinical studies will be covered, reviewing evidence for neurotoxicity and then clinical research on chronic effects of ketamine and PCP- which is at this stage is confined to recreational drug users- will be considered

PART I: ACUTE EFFECTS OF NMDA-R ANTAGONISM ON COGNITIVE FUNCTION

1.9.1 Animal studies of cognitive function after acute administration of NMDA-R antagonists

There has been an abundance of research concerning learning and memory in animals following NMDA-antagonist administration (See Morris & Davis, 1984 for a review). This will be only briefly addressed as a background to the human research, which is the focus of this review. The rationale for much of this work has been to investigate the link between LTP and the behavioural correlates of learning and memory in animals. Whilst much of the preclinical research has been conducted with the selective NMDA-R antagonist AP5, work has also been carried out with ketamine, PCP and MK-801. These drugs were considered ideal tools with which to block hippocampal LTP in vivo and so investigate the effect of this antagonism on synaptic plasticity (Morris & Davis, 1994). The finding that NMDA-R antagonists can block learning at concentrations similar to those that block LTP in vitro (Davis et al., 1992) was considered further evidence for the link between hippocampal LTP and learning in animals.

It has been well established that spatial learning in paradigms such as the Morris Water Maze is disrupted after competitive and non-competitive NMDA-R antagonist administration in rats and cats (Balster & Chait, 1976; Davis et al. 1992; Handelman et al., 1987; Morris et al., 1990; Spangler et al., 1991). Spatial learning tasks are dependent on the integrity of the hippocampus (O'Keefe & Nadel, 1978) in which LTP was first discovered and investigated (Bliss & Lomo, 1973). Thus, this work further supports the idea that hippocampal LTP may be involved in learning and memory. In rodents, the deficit in memory function induced by NMDA antagonists appears to involve an impairment in the acquisition or encoding of new information rather than its retrieval (Spangler et al. 1991). In non-human primates similar impairments have been reported (Frederick et al., 1995; Thompson et al., 1987) again suggesting impairments of encoding rather than retrieval of new information (Buffalo et al., 2002).

Research has further demonstrated deficits in performance on the delayed non-matching to sample task designed to tap working memory, after administration of an NMDA receptor antagonist in rats (Lyford et al., 1993). In non-human primates, acute PCP administration impairs performance in a similar delayed non-matching to sample task of working memory task, but in a delay independent fashion (Boyce et al., 1991).

Administration of ketamine, PCP and MK-801 has also been shown to impair performance on amygdalar and simple associative learning tasks such as acquisition of a conditioned emotional response (Hoehn-Saric et al., 1991), flavour aversion (Aguado et al., 1994), an operant response (Pallares et al., 1995) or conditioned cue preference (Stevens et al., 1997). Deficits in conditional discrimination tasks (Moerschbaecher & Thompson, 1980) and tasks that measure motivation (Frederick et al. 1995) have also been observed. In summary, NMDA-R antagonists produce wide-ranging deficits in pre-clinical models of cognition, most notably in paradigms thought to depend upon the integrity of the hippocampus and amygdala.

1.9.2 Memory Systems and NMDA-R Hypofunction

In 1994, Schacter and Tulving published an influential essay on memory systems. This summarised the main proposed systems of memory up to that time Tulving defined a memory system in general as "a set of correlated processes" (Tulving, 1985 p.386, c.f. Schacter, 1999). Differing memory systems have been identified by their representation of different kinds of information, in addition to distinct neurobiological underpinnings. Separate memory systems were suggested to have different laws and principles characterising their operation and differences in their ontogenetic and phylogenetic development (Schacter, 1999). The memory systems model was developed from the findings of cognitive, neuropsychological, psychopharmacological and more recently neuroimaging research. The five proposed memory systems are: episodic memory, working memory, semantic memory, procedural memory and the perceptual representation system. This framework, including Baddeley's (2000) conceptualisation of working memory, will be used in this review for examining the evidence concerning the mnemonic consequences of NMDA-receptor antagonism.

An important caveat to consider before examining research into ketamine's effects on memory systems, is that no one task can tap a single memory system or process. The five systems to be discussed below are interactive and one task may involve two or three memory systems. For example in immediate prose recall, the recency effect (better memory for most recently presented material) involves aspects of working memory and yet the primacy effect (better memory for material presented first) probably involves episodic memory, whereas understanding the meaning of the prose is a function of semantic memory. With this caveat in mind, the findings of studies reviewed below are summarised in Table 1.1. in terms of the principal system thought to be tapped by the task employed. Other factors that complicate comparisons between the studies reviewed below include I) the wide variety of tasks used across the different studies II) the wide variety of doses, routes of administration and populations III) the variation in test times post-ketamine that have been used. Further differences have also been observed that are not accounted for by the above explanations (see Honey et al., 2003). These may be related to individual differences in drug response (e.g. Malhotra et al., 1998) or the use of different strategies to meet task demands that may vary from subject to subject (Honey et al., 2003). Despite this however there is sufficient commonality in the studies to allow comparison, and the memory systems framework is useful conceptually in the examination of these studies.

1.9.3 Episodic Memory

Episodic memory makes possible what Tulving (1998) terms 'mental time travel' back into a person's past. It facilitates the acquisition and retrieval of information about specific personal experiences that occur at a particular time and place (Tulving, 1985b; Tulving & Markowitsch, 1998). A large number of studies have consistently found ketamine-induced decrements across tasks which principally tap episodic memory at a range of doses (Hetem et al., 2000; Ghoneim et al., 1985; Krystal et al., 1994; Malhotra et al., 1997a; Newcomer et al., 1999). In addition, these effects have been found across diverse measures, including recognition tasks (Hetem et al., 2000; Ghoneim et al., 1985; Honey et al., 2003), recall of passages of prose (Newcomer et al., 1999), recall of high and low frequency word lists (Hetem et al., 2000; Ghoneim et al., 1985; Malhotra

et al., 1996), spatial learning paradigms (Rowland et al., 2005) and, of particular relevance to episodic memory, source memory tasks (Honey et al., submitted) .

Other studies have investigated the relative contributions of encoding and retrieval to these verbal episodic memory deficits. Ghoneim et al. (1985) reported that acute ketamine (0.25mg/kg and 0.5mg/kg) produces significant dose dependent impairments in delayed recall of word lists learnt both pre and post drug administration in healthy volunteers; they concluded that ketamine impairs retrieval and not encoding. However, this study did not maintain a steady state infusion, and participants were tested on the pre-drug words shortly after a bolus when they were highly dissociated. In addition, practice effects and differing duration and nature of retention intervals between each testing complicates interpretation of these data. Further work appears to contradict these findings. Hetem et al. (2000) looked at recall of words learnt before and after drug administration and found that recall was only significantly impaired for words presented post-drug. A similar impairment in memory of information learnt post-infusion has been noted on recognition memory tasks (Hetem et al., 2000; Honey et al., submitted) and a virtual Morris water maze (Rowland et al., 2005). Pre-clinical support for ketamine-induced encoding impairment (discussed in section 1.9.1.) is provided by studies describing NMDA antagonist-induced deficits in acquisition (i.e. encoding) but not performance (i.e. retrieval) in spatial learning tasks (Ohno et al., 1994). Indirect evidence from another study (Malhotra et al., 1996) suggests that ketamine preferentially impairs encoding processes. Ketamine produces decrements in both free recall and recognition. Impaired recognition implies impaired encoding. The reasoning behind this being that recall, but not recognition, performance requires retrieval processes in searching for information in memory. The latter findings may also be interpreted in terms of the recollection / familiarity distinction discussed below.

Another facet of verbal episodic memory, the conscious state associated with remembering, also appears to be affected by ketamine. Memory research has promoted the view that episodic memory may be characterised by the subjective awareness of recreating events and experiences and reliving these events and experiences mentally. Tulving (1985) termed this type of awareness 'autonoetic' awareness and contrasted it

with 'noetic' awareness, that is feelings of *familiarity* with an event or experience without conscious *recollection.* This can also be thought of as the difference between 'remembering' and 'knowing'. Ketamine has been found to decrease remember and know responses, but not to selectively affect any particular state of awareness in recognition compared to controls (Hetem et al., 2000). This is an interesting finding in that several clinical populations, e.g. schizophrenic patients (Huron et al., 1995), amnesics (Knowlton & Squire, 1995), Alzheimers patients (Schacter et al., 1997) and psychopharmacological studies with amnestic agents such as lorazepam (Curran et al., 1993) and alcohol (Curran & Hildebrandt, 1999) have demonstrated preserved 'know' responses but reduced remember responses. The original theory relating to autonoetic awareness proposed by Tulving (1985) was that remembering responses are best accounted for by episodic memory and know responses by semantic memory. The results of Hetem et al.'s study could be explained by the preliminary evidence of semantic memory deficits found with ketamine which are discussed further below, in section 1.2.5. However, a complication in the design of the task in the Hetem et al. study was that the recognition test did not include lures, or new items, therefore the post-drug differences could be explained in a change in bias of responding (Honey et al., submitted). A subsequent study, however, found evidence suggesting impaired recollective ('remember') processes in the face of preserved familiarity ('know') suggested by preserved memory for shallowly and deeply encoded words but impaired memory for words encoded at an intermediate level (Honey et al., submitted) which casts doubt over Hetem et al.'s findings.

Recent neuroimaging data have also shed light on processes involved in episodic memory following ketamine. Compared to placebo at encoding of subsequently successfully remembered words, a dose of ketamine produced an increase in left frontal activity on a deep encoding task, as estimated by the BOLD signal (Honey et al., 2005). The authors interpreted this finding as difficulties in selecting semantic attributes relevant to the semantic judgement that constituted the deep encoding task. In addition, they observed increased right lateral prefrontal cortex activation which may reflect incidental non-verbal processing (Honey et al., 2005). At retrieval, ketamine affected hippocampal and frontal activity. Decreased left prefrontal response was observed, which the authors suggest may indicate a failure to retrieve contextual detail associated

with stimuli. Increased BOLD response in the bilateral PFC and right hippocampus was also observed. This may indicate the more demanding nature of retrieval on ketamine and reduced access to contextual details. ACC activation was also greater to incorrect responses, on placebo this was reduced in relation to correct trials. The ACC is thought to be involved in error monitoring, thus this may indicate deficient error monitoring on ketamine. It is worth noting that these changes were observed in the absence of any behavioural impairment. This highlights how imaging may be useful in demonstrating subtle differences which are not apparent on behavioural tasks. Making the presupposition that BOLD signal changes reflect changes in underlying neural activity, the authors also note however that without performance differences it is difficult to ascertain whether greater activation reflects increased glutamatergic activity at non-NMDA receptors, and possibly enhanced function or whether this reflects a compensatory mechanism for inefficient processing.

1.9.4 Working Memory, Attention and Executive functioning

Working memory is proposed to facilitate the maintenance and manipulation of internal representations such that these representations can be used to guide future behaviour (Baddeley, 1998). The most recent form of the model is comprised of four components: the phonological loop, the visual-spatial scratchpad, the central executive and the episodic buffer (Baddeley, 2001). Baddeley suggests that the phonological loop is involved in rehearsal and temporary storage of auditory verbal information and that the visual-spatial scratchpad serves an analogous function for visual and spatial properties of a stimulus (these two are termed 'slave systems'). The central executive is thought to be a limited capacity supervisory attentional mechanism (Shallice, 1982) and the episodic buffer, the newest component of the model, is proposed to facilitate the integration of information from all of the above sources and long-term memory.

Forwards digit span, which involves repeating back a sequence of numbers, may be seen as an index of the phonological loop. Performance on this task is intact following ketamine adminstration (Ghonheim et al., 1985; Honey et al., 2003; Rowland et al., 2005; Abel et al., 2003). From the limited evidence available - one study examining forwards spatial span (Rowland et al., 2005) and a spatial delayed response task

Principal memory system tapped	Task	Study	
Episodic Memory	Immediate verbal recall	Ghoneim et al. (1985),	X
		Krystal et al. (1994)	√
		Harborne et al. (1996)	X
		Malhotra et al. (1996)	X
		Newcomer et al. (1999)	X
		Hetem et al. (2000)	X
	Delayed verbal recall	Ghoneim et al.(1985)	X
		Krystal et al. (1994)	X
	Verbal recognition	Ghoneim et al. (1985)	X
		Malhotra et al. (1996)	X
		Hetem et al. (2000)	X
		Honey et al. submitted	X
	Source Memory	Honey et al. submitted	X
	Spatial Memory	Rowland et al. (2005)	X
	Associative Memory	Harris et al. (1975)	X
		Harborne et al. (1996)	X
	Category Fluency	Ghoneim et al. (1985),	√
		Adler et al. (1998)	X
Semantic memory	Digit span	Harris et al.(1975)	√
	(forwards / backwards)	Ghoneim et al. (1985)	√ √
		Honey et al. (2003)	√ X
		Abel et al. (2003)	√ X
		Rowland et al. (2005)	√ √
Working Memory	Spatial Span	Rowland et al. (2005)	√
	N-back – 1-back, 2 back	Newcomer et al. (1999)	X
	Spatial working memory (SDR)	Newcomer et al. (1999)	√

Principal memory system tapped	Task	Study	
Attention	CPT	Krystal et al. (1994)	X
		Harborne et al. (1996)	√
		Malhotra et al. (1996)	X
		Adler et al. (1998)	√
		Newcomer et al. (1999)	√
		Umbricht et al. (2001)	X
	N-back – 0-back	Newcomer et al. (1999)	√
	Stroop	Harborne et al. (1996)	√
		Newcomer et al. (1999)	√
	DSST/ SCT	Hetem et al. (2000)	X
Executive Functioning	Verbal fluency	Krystal et al. (1994),	X
		Krystal et al.(1997)	X
		Adler et al. (1998),	X
		Newcomer et al. (1999)	√
		Krystal et al.(1999)	√
		Abel et al. (2003)	√
		Rowland et al. (2005)	√
	Trailmaking	Harborne et al. (1996) A-B	√
	WCST	Krystal et al. (1994)	X
	Tower of London	Honey et al. (2003)	√
Procedural Memory		No studies	??
PRS		No studies	??

Table 1.1. Findings of studies administering an acute dose of ketamine to healthy volunteers, summarised in terms of the 'memory systems' model.

(Newcomer et al., 1999)- the operations of the visual-spatial scratchpad also seem to be unaffected by ketamine.

Ketamine's effects on integration and manipulation within working memory, i.e. the central executive, have also been investigated although findings are less consistent than those relating to the slave systems. Preserved backwards digit span has been observed in some (Rowland et al., 2005; Ghonheim et al., 185; Harris et al., 1975), but not all (Honey et al., 2003; Abel et al., 2003) studies. Neuroimaging work has demonstrated augmented BOLD response on ketamine in frontal-parietal regions for manipulation but not maintenance of information (Honey et al., 2004). This suggests that in the former studies, even when no behavioural differences are present, manipulation of information in working memory by the central executive is affected by ketamine, although again it is unclear what exactly this may reflect i.e. augmented or decreased glutamatergic activity and/or performance.

Adler et al. (1998) used the n-back to tap working memory. This involves an attentional component (0-back) where participants are required simply to respond to a particular number/ letter and then two further components with increasing working memory load. In the 1-back, participants are required to respond if the letter/number is the same as the one previously presented; in the 2- back they must respond if the letter/number is the same as the one two before. Ketamine was associated with decreased scores on the one-back and two-back, but not the zero back, components. Conversely, spatial working memory was preserved after ketamine administration (Honey et al., 2003). However this finding was complicated by the presence of only one version of the spatial working memory task within the CANTAB, thus this finding may have been confounded by more complicated order x drug interactions in this repeated measures design. On the serial seven's task, which may also tap the episodic buffer, impaired performance after PCP administration has been observed (Cohen et al., 1962; Luby et al., 1959).

Results from investigations into ketamine's effects on sustained attention are again relatively equivocal. Some studies report ketamine-induced deficits in sustained attention on the continuous performance task (CPT: Krystal et al., 1994; Malhotra et al.,

1996) but others report no deficits (Krystal et al., 1999; Newcomer et al., 1999). Intriguingly, relatively specific deficits have been found on the 'AX'- version of the CPT. This task assesses both sustained attention and the successful processing of task relevant cues. Subjects are required to respond to the letter 'X' only when it is preceded by an 'A'. Distractor trials in the task include an 'A' followed by a 'Y' or 'B' followed by an 'X' or a 'Y'. Ketamine decreased hit rates (on 'A-X' trials) and also increased the number of 'B-X errors on this task (Umbricht et al., 2000). The specificity of these errors may reflect an inability to use contextual cues appropriately, rather than an indiscriminate increase in errors, as other types of errors (AY and BY) were similar across groups. In contrast to the work on sustained attention, studies that have examined selective attention using the Stroop paradigm have, in general, found it to be unimpaired (Harborne et al., 1996; Newcomer et al. 1999; Oranje et al., 2000; Rowland et al. 2005) . In light of the attentional difficulties observed it is plausible that these may underpin some of the other cognitive deficits observed following ketamine. Malhotra et al. (1996) covaried for attentional effects and found ketamine's effects on memory (free recall and recognition) were still significant.

Working memory is also conceptualised under the umbrella term of 'executive functions'. Executive functioning can be conceptualised as the selection, monitoring and integration of cognitive and behavioural processes and is served by the frontal lobes. After ketamine administration participants made more perseverative errors on the Wisconsin Card Sorting task (WCST; Krystal et al., 1994) which is thought to tap executive functioning. Krystal et al. (2000) re-examined performance on the WCST by repeating the task following ketamine and placebo in a crossover design. Participants who had acquired the rules of the WCST whilst on ketamine performed worse in the task whereas those who acquired the rules on placebo were relatively unimpaired. The authors suggested that general NMDA-receptor mediated impairments to learning do not affect the cognitive functions necessary to carry out the WCST such as mental set-shifting and that impairments on this task may reflect more general deficits in rule learning (Krystal et al., 2000). This may be of relevance for findings of the effects of ketamine on the Tower of London task, where no impairment was observed following ketamine (Honey et al., 2003). Again, this task is not intended to be repeated as strategies can be acquired and in repeated measures designs complex order by drug

interactions may occur. Executive functioning has been further examined with a simple trailmaking task by Harborne et al. (1996) who found preserved frontal functioning (Trails B), once psychomotor slowing (Trails A) had been controlled for. Fluency is also considered to be a task tapping executive functions, and may involve the putative 'episodic buffer', but will be discussed below as a semantic memory task as this is how it has been classified in the majority of the ketamine studies that have employed it.

1.9.5. Semantic Memory

Semantic memory refers to a person's general knowledge about the world (Tulving, 1972). It differs from episodic memory in that semantic information is not associated with a specific learning context. Semantic knowledge covers a range of organised information including concepts, vocabulary and facts. Prior to some of the studies in this thesis, effects of ketamine on semantic memory had been explained only with fluency tasks and findings were inconsistent. Whilst some studies showed ketamine-induced impairments in category (Abel et al., 2003a; Adler et al., 1998) and phonemic fluency (Adler et al. 1998; Krystal et al., 1994; Krystal et al., 1999b) tasks, others have found fluency to be intact (Abel et al. 2003a; Newcomer et al. 1999; Rowland et al. 2005; Krystal et al. 1999b). Overall the existence of semantic memory deficits following ketamine administration would appear to still be in debate.

1.9.6 Procedural Memory and Perceptual Representation System (PRS)

Procedural memory and the PRS are non-declarative memory systems where retention is assessed indirectly or implicitly. Procedural memory pertains to the learning of motor and cognitive skills; 'real-world' examples may be learning to ride a bike or learning to read. Procedural memory is likely comprised of numerous subsystems with the commonality between them being that they all consist of learning a new skill. No research prior to this thesis had investigated the effect of NMDA-R antagonism on procedural memory. Ketamine was administered on a repeated version of WCST (Section 1.9.4) and findings implied an impairment in acquisition but not expression of the rules necessary to conduct the task. These data may relate to procedural memory

impairments but as the WCST is not a procedural task *per se*, it is difficult to draw any conclusions.

The perceptual representation system can be viewed as operating on perceptual information about the form and structure of words and objects. In memory research the main interest in the PRS relates to its role in perceptual priming. Perceptual priming refers to an increased likelihood of identifying or remembering an object as a result of previous exposure to it. This relates additionally to implicit memory, or memory when stimuli are presented and recalled without awareness. No studies had investigated perceptual priming with NMDA-R antagonists.

1.9.7.Summary of acute cognitive effects

NMDA-R antagonists produce impairments in episodic-like memory. These deficits appear to be a result of encoding rather than retrieval failures. The central executive component of working memory may be impaired by ketamine, whilst slave systems are left intact. There is some evidence of semantic impairments following ketamine. Priming and procedural memory have not been investigated with NMDA-receptor antagonists. Cognitive impairments following NMDA-R antagonist administration have been found to be wide-ranging and yet there are still many gaps in our knowledge. As cognitive impairments have been used to support the NMDA-R hypofunction / glutamatergic hyperfunction model of schizophrenia discussed below it is also important to fully characterise these impairments to assess the degree to which ketamine and related compounds provide a good model of the cognitive deficits associated with schizophrenia.

PART II: SCHIZOPHRENIC SYMPTOMS AND NMDA-R ANTAGONISTS

First described by Kraeplin (1893) as 'dementia praecox', schizophrenia is a widespread and disabling disorder prevalent in about 1% of the population worldwide (NICE, 2002). Gaining a thorough understanding of the symptoms and aetiology of the

disease remains one of the greatest challenges in psychiatric research. Symptoms of schizophrenia can be divided broadly into three groups: *'positive' symptoms* such as delusions, disorganised thinking and speech, hallucinations, altered perceptions and inappropriate affect; *negative or deficit symptoms* such as poverty of speech, blunted and flat affect, loss of volition and social withdrawal; *cognitive symptoms* including thought disorder, incoherence, looseness of associations and neologisms.

1.10.1 Background to theories of cognitive dysfunction in schizophrenia

Along with the symptoms described above, patients with schizophrenia exhibit a variety of cognitive deficits including impairments in executive functioning, attention, working, episodic and semantic memory (Heinrichs & Zakzanis, 1998). These deficits are relatively resistant to anti-psychotic medication (Calev et al., 1983; McKenna et al., 1990), are observed in the unaffected twins of monozygotic pairs (Goldberg et al., 1993), and can precede the onset of schizophrenia and predict the development of symptoms in people who score highly on schizotypy (or psychosis proneness) scales (Friedman & Chapman, 1973). Some memory functions are relatively well preserved in schizophrenia however, with a crucial determinant appearing to be conscious awareness at retrieval (Danion et al., 1999; Danion et al., 2001; Gras-Vicendon et al., 1994; Huron et al. 1995). Patients with schizophrenia exhibit impaired retrieval on explicit memory tasks such as recall and recognition of word lists but, in general, have intact implicit memory or learning (Huron et al., 1995; Danion et al., 2001).

Several theories have suggested that cognitive deficits in schizophrenia may underlie symptomatology, in particular, negative symptoms. Neuropsychological theories of schizophrenic symptoms include an impairment in working memory and prefrontal lobe functioning (Goldman-Rakic, 1988) and a weakening of the influences of stored memories on current perception (Hemsley, 1987) with links proposed between this abnormality and latent inhibition (Lubow et al., 1982). Frith (1987) proposed that the two syndromes of schizophrenia are due to different impairments in the initiation of action. Type I, or acute schizophrenia with positive symptoms is thought to be a product of inappropriate monitoring of the source of willed intentions and actions. Type II, or chronic schizophrenia with negative symptoms is hypothesised to be a deficit in

forming willed intentions. Frith (2002) extended his monitoring theory to suggest that the inability to monitor willed intentions can lead to hallucinations, delusions of control and thought insertion, as a result of attributing internal thought and action to external sources. Paranoid delusions and ideas of reference are also conceptualised as deficits in monitoring of beliefs and intentions of others. However, it seems at best ambitious to suppose that a single theory could account for the heterogeneity of symptoms in schizophrenia.

Research has been largely unsuccessful in demonstrating a correlation between positive symptoms and neuropsychological impairments. This could be a result of the lack of sensitivity of cognitive tests which often tap a variety of cognitive functions, or the suggestions that cognitive symptoms often persist after the remission of acute positive symptoms in schizophrenia. The case for a relationship with negative symptoms is stronger but there is danger of circularity with these symptoms e.g. verbal fluency impairments are correlated with poverty of speech (Phillips & David, 2000). Given the ability of NMDA-R antagonists to induce schizophrenia-like symptoms and the role of the NMDA-R in learning, it is tempting to speculate that a common process may mediate some of the cognitive dysfunction of schizophrenia and that induced by NMDA-R antagonists.

1.10.2 Schizophrenia and NMDA-R Antagonists

Within psychiatric neurobiological research, several methods of inducing psychotic symptoms in animals and humans have been used. These include in animals, chronic social isolation or stress (Jones et al., 1990) and perinatal insults (Lipska et al., 1993; Moore & Grace, 1997) and in both humans and animals, sleep deprivation (Patat et al., 1999) and the administration of psychotomimetic drugs (Javitt & Zukin, 1991; Snyder, 1988). Due to the transience of symptoms and cross-species applicability, one of the most popular methods of inducing psychosis in animals and humans is the latter.

Recently, interest in the potential use of non-competitive NMDA-receptor antagonists as models of the symptoms, and possibly the aetiology, of schizophrenia has grown. During the 1950's many researchers considered lysergic acid diethylamide (LSD) to be

a good pharmacological induction of psychosis (Vollenweider et al., 1998). However, this came to be viewed a superficial model that a well-trained observer could easily discriminate from true psychosis (Hollister, 1962). A further popular drug model was stimulant psychosis, precipitated by chronic amphetamine or cocaine use. Long-term amphetamine use induces a form of paranoid psychosis with positive symptoms. In addition, high-dose repeated administration of amphetamine to healthy volunteers can induce paranoid symptoms that mimic the symptoms of paranoid schizophrenia (van Kammen et al., 1982). Indeed, the amphetamine model, along with evidence from Parkinson's patients (Bunney, 1970), contributed to the dopamine hypothesis of schizophrenia which led to the development of phenothiazines and other D2 receptor antagonists as drug treatments for the disorder. However, while the LSD and chronic stimulant models can induce some of the positive symptoms of schizophrenia, evidence of any true 'deficit' state in either model is conflicting (Angrist & Gershon, 1970) . In contrast, non-competitive NMDA-R antagonists like ketamine and PCP appear to be able to induce both the positive and negative symptoms of schizophrenia (Bakker & Amini, 1961; Malhotra et al., 1996).

The ability of PCP to produce a psychosis 'indistinguishable' from acute schizophrenia was first observed in the late 1950's (Luby et al., 1959) and then replicated in the early 1960's (Bakker & Amini, 1961; Cohen et al., 1962; Davies & Beech, 1960). Due to the duration of effects and neurotoxicity of PCP, controlled studies of PCP in humans are now prohibited, however animal research with PCP and its stronger congener dizocilipine have continued. In addition, several preclinical and clinical studies have used ketamine to elicit a 'model psychosis'.

A clear and insurmountable problem for animal 'models' of schizophrenia, is the inability to produce certain symptoms associated with the disorder such as those associated with verbal behaviour (for example auditory hallucinations). In their review of the area, Geyer and Markou (1994) highlight the difficulties of achieving even face validity, let alone construct validity in an animal model of schizophrenia. With this caveat in mind, the animal literature that has measured behaviours thought to resemble the symptoms of schizophrenia with NMDA-R antagonists will be briefly reviewed, before moving on to more extensive coverage of the human literature.

1.10.3 Animal models of other psychotic symptoms

Ketamine, PCP and MK801 administration have been reliably shown to induce hyperlocomotion in rats (Boyce et al., 1983; Moghaddam & Adams, 1998). PCP has also been shown to inhibit dopamine reuptake which, it has been suggested, may in part be responsible for stereotypies and locomotor stimulation in rats (Johnson, 1983). However hyperlocomotion has been criticised for not being a reliable indicator of any specific schizophrenic symptomatology (Jentsch & Roth, 1999). At higher doses, PCP and related compounds have been shown to induce profound tranquillisation, similar to dissociative anaesthesia in humans. This tranquillisation resembles a catatonic state which invokes parallels with schizophrenic catatonia. In monkeys, PCP tranquillisation is so profound that experimenters are able to put their fingers in the monkey's mouth while its eyes are open (Chen & Weston, 1960). PCP has been shown to reduce social interaction in rats, however this could be secondary to more general motor and arousal deficits. Much effort has been devoted to characterising the 'cognitive' impairments associated with PCP, MK-801 or ketamine administration in animals often focussing on spatial and working memory deficits as described in section 1.2.1., which could be tenuously linked to the cognitive dysfunction observed in schizophrenia.

One of the broad spectrum of symptoms experienced by people with schizophrenia is an inability to filter or 'gate-out' irrelevant thoughts and sensory stimuli from conscious awareness. A paradigm used to investigate these gating difficulties is prepulse inhibition (PPI). PPI refers to a decreased startle response to an intense stimulus when it is preceded by a weaker stimulus (or prepulse). PPI has been extensively investigated in schizophrenics where deficits in PPI have been found when compared to normal or psychiatric controls (see Braff et al., 2001 for a review). Moreover PPI can be readily modelled in animals as it is a cross-species phenomenon.

As interest in the NMDA-R hypofunction model of schizophrenia has grown, increasing numbers of studies have investigated PPI following ketamine, PCP and MK-801 administration in animals. Mansbach and Geyer (1989) first demonstrated that PCP and dizocilipine decrease PPI in rats. These findings have since been replicated in many studies (Zhang et al., 1997; Bakshi & Geyer, 1995; Depoortere et al., 1999). The effects

on PPI were obtained at doses lower than those required to affect locomotor activity, indicating a robust and potent PPI effect. However in the first study (Mansbach & Geyer, 1989), ketamine was not observed to disrupt PPI. Despite this, every subsequent study has demonstrated a decrease in PPI in rats following the administration of ketamine (e.g. Mansbach & Geyer, 1991; Swerdlow, 1998; Johansson et al., 1995). Factors that may account for the discrepancy between these initial findings and all following studies could be wider ranges of stimulus intervals, doses and injection to test intervals (Geyer et al., 2005).

1.10.4. Human studies of psychotic symptoms following NMDA-R antagonism

Human research examining the psychotomimetic properties of non-competitive NMDA-R antagonists is confined to ketamine, with the exception of the few early PCP studies mentioned in Section 1.1. above. The first study to fully characterise psychotic symptoms associated with ketamine administration, with the Brief Psychiatric Rating Scale (BPRS- Overall and Gorham, 1962), was conducted by Krystal et al. (1994). Four key items were chosen to index positive symptoms: conceptual disorganisation, hallucinatory behaviour, suspiciousness and unusual thought content. They additionally used 3 key items to examine negative symptoms: blunted affect, emotional withdrawal and motor retardation and extracted 2 other factors of hostility-suspiciousness and activation from the BPRS overall score. Krystal et al. (1994) found an increase following ketamine (0.5 mg kg^{-1}) on all four positive symptoms, but no change at a lower dose (0.1 mg kg^{-1}). However, the hallucinatory behaviour recorded was only illusory experiences, mainly confined to the visual domain, which are not classified as hallucinations in the BPRS. Ketamine was also reported to dose dependently increase all three key negative symptoms in this study. However despite high clinician ratings, the paper also states that in several subjects "...ketamine evoked intense emotional responses..." (pp.204; Krystal et al., 1994). It is not clear the degree to which general psychomotor retardation and sedation may have been confounded with the clinician rating of emotional withdrawal, motivational deficits and blunted affect. Ketamine was also reported to increase behavioural activation and hostility-suspiciousness but only in the 0.5 mg/kg group. Perceptual distortions on both the Clinician Administered Dissociative Scale (CADSS) and the Perceptual Aberration Sub-scale of the Wisconsin Psychosis Proneness scale (WPP) were dose dependently increased. Interestingly, the

self-rated PAS and the clinician rated items of the CADSS which both measure perceptual distortions were not correlated on the test day, perhaps indicating a discrepancy between the clinician ratings and subjective ratings. A problem with the BPRS may be that it may not be sensitive to some subtle psychotomimetic drug effects as it focuses on only some of the range of psychotic symptoms. It is also difficult to administer to patients who are very withdrawn or mute, as participants on ketamine may become.

Several other studies have since replicated the findings of elevated total BPRS scores following ketamine challenge (Adler et al., 1998; Duncan et al., 2001; Hetem et al., 2000; Malhotra et al., 1996; Newcomer et al., 1999; Oranje et al., 2000; Umbricht et al., 2000; Umbricht et al., 2002; van Berckel et al., 1998). However, some have shown slight departures from the original findings. Malhotra et al., (1996) found significant increases in the factors of withdrawal-retardation and thought disorder but not anxiety-depression and hostility-suspiciousness. In a study of healthy volunteers, ketamine produced increases in the Assessment of Thought, Language and Communication (TLC) total score and on the verbal productivity and disconnection factors of the TLC (Adler et al., 1998). In this study, ketamine produced significantly a higher total score on the BPRS but the only factor where a significant difference was detected after ketamine was thought disorder. The same research group (Adler et al., 1999) validated the NMDA-R antagonist model by comparing thought disorder in schizophrenic patients to that induced by ketamine. They found no significant differences thus providing support for the NMDA-R hypofunction model of thought disorder.

The link between cognition and ketamine-induced schizophrenic-like symptoms has also been investigated. Malhotra et al. (1996) further attempted to correlate the psychiatric symptoms with cognitive effects but found no relationship of either thought disorder or withdrawal-retardation with free recall or recognition memory scores. However, a subsequent study did find a relationship between elevated positive symptoms following ketamine and recognition memory impairment (Hetem et al., 2000) although problems with the recognition memory design of this study (discussed previously) complicate interpretation of this correlation. In addition, scores on the TLC were found to correlate with the 1-back test of working memory (Section 1.9.4.) but not

the 2-back test or fluency scores (Adler et al., 1998). The authors interpreted this as tentative support for the relationship between working memory and thought disorder and evidence against the putative involvement of semantic memory in thought disorder. This interpretation is, however, complicated by no correlation on the 2-back task. This is the most difficult component of this working memory task and thus the lack of correlation may be attributable to floor effects in the ketamine group. However, a subsequent study found evidence of elevated thought disorder in the absence of working memory impairment, which casts doubt over the putative link between the two (Newcomer et al., 1999). LaPorte et al. (1996) also found no impairment to either semantic or phonemic fluency performance in schizophrenic patients following ketamine challenge; however, these findings are hard to interpret given schizophrenia is associated with semantic memory deficits. It is possible that elevated baseline semantic memory impairments meant that the verbal fluency and category generation tasks were not sensitive enough to pick up ketamine induced changes. Furthermore participants were tested 45 min after administration of a ketamine bolus. Previous research suggests that the cognitive effects of ketamine in schizophrenic patients remit about 30 min after bolus drug administration (Malhotra et al., 1996).

The effects of non-competitive NMDA-R antagonists on PPI in humans have been examined in parallel to the preclinical work reviewed above. In contrast to pre-clinical observations, findings from ketamine challenge in humans have been largely inconsistent. The first study to examine the effects of NMDA-R antagonism on PPI in humans (van Berckel et al., 1998) used a low dose of ketamine (0.3mg/kg) and a pseudo steady-state infusion. This dose was chosen to minimise μ-opiate receptor effects and resulted in increases in blood pressure, cortisol levels and heart rate, consistent with ketamine effects. Although this dose of ketamine induced a small increase in total scores on the BPRS, it did not significantly alter PPI. This may be a function of the low dose used (van Berckel et al., 1998). Subsequent studies using higher dose of ketamine have found no effect on PPI (Duncan et al., 2001) or in some cases slight increases (Abel et al., 2003). Possible reasons for differences between these studies and the animal work are the higher doses used in preclinical studies and differences in drug metabolism between humans and animals. Moreover, drug-induced psychosis in humans is a more efficient model of the acute phase of schizophrenia than

chronic stages (Gouzoulis-Mayfrank et al., 1998a) and yet all studies of PPI in schizophrenia have focused on chronic patients (Geyer et al., 2005). Furthermore, PPI is not a model of schizophrenia merely of the sensorimotor gating deficits associated with it.

1.10.5. Administration of NMDA-R antagonists to schizophrenic patients

Further support for the involvement of glutamate in the pathophysiology of schizophrenia derives from symptom provocation studies involving NMDA-R antagonists. PCP induces a prolonged exacerbation of psychotic symptoms in patients which resembles the acute phase of their illnesses (Luby et al., 1959; Ban et al., 1961). Studies have also shown increases in positive symptoms in schizophrenics following ketamine challenge, both with patients on haloperidol (a DA antagonist) (Lahti et al., 1995b; Lahti et al., 2001) and neuroleptic-free patients (Lahti et al., 1995; Malhotra et al., 1997; Lahti et al., 2001). Neuroleptic free patients in the latter studies reported a recurrence of auditory hallucinations during the ketamine infusion and high levels of paranoia whereas none of the healthy volunteers reported auditory hallucinations and only one healthy volunteer reported feelings of suspiciousness. In the haloperidol group (Lahti et al., 1995), many of the positive symptoms induced by ketamine were similar the patient's own acute symptoms. It has been suggested that other drug models of psychotic symptoms are more prone to stereotyped responses that do not vary from patient to patient (Pennes, 1954). The ability of ketamine to induce symptoms that resemble the patient's original illness, and can vary from patient to patient, suggests a close link between glutamatergic transmission and schizophrenia. BPRS change scores were not significant between neuroleptic free patients and healthy volunteers, however this may be due to inherent difficulties in equating a change in rating of none to mild symptoms with a change of moderate to severe symptoms on the BPRS (Malhotra et al., 1997b). It is noteworthy only one study observed increases in negative symptoms in schizophrenic patients after ketamine challenge (Malhotra et al., 1997). The absence of negative symptoms in other studies (Lahti et al., 2001; Lahti et al., 1996) could be due to different drug administration i.e. bolus versus continuous infusion. The authors also speculate that this could be due to desensitisation of ketamine's effects on mental state

in the presence of endogenous psychosis. As noted above, differences in medicated and unmedicated schizophrenic patients have been observed. Further studies have explored the interactive effects of ketamine with other drugs as a way of elucidating the influences of different neurotransmitter systems in the psychotomimetic effects ketamine or with the eventual aim of developing antipsychotic medication.

1.10.6. Interactive effects of ketamine with other drugs

Several drugs have been reported to reduce the emergence phenomena associated with ketamine anaesthesia. The benzodiazepines (BDZs) modulate the actions of the inhibitory neurotransmitter γ-aminobutyric acid (GABA) and some lines of evidence would suggest an interactive effect with NMDA-R antagonists. Studies have demonstrated that abnormal GABA transmission may have a role to play in the pathophysiology of schizophrenia. For example, studies of schizophrenics have demonstrated lower GABA uptake and release in the frontal cortex (Simpson et al., 2005). Furthermore, preclinical studies have demonstrated that NMDA-antagonists reduce GABAergic inhibition in the cortex (Dingledine et al., 1986) and BDZs reduce NMDA-R antagonist stimulation of frontal cortical DA turnover (Bower & Morton, 1992). BDZs have also been shown to have a weak preventative effect on NMDA-R antagonist neurotoxicity (discussed below) (Olney et al., 1991).

Pre-medication with diazepam (Kothary & Zsigmond, 1977; Tucker et al., 1984), flunitrazepam (Freuchen et al., 1976), lorazepam (Dundee & Lilburn, 1978) or midazolam (White et al., 1982; Renstall, 1988) is effective in preventing dysphoria and psychotic symptoms upon emergence from ketamine anesthesia (Zsigmond & Domino, 1980). Conversely, administration of the BDZ inverse agonist flumazenil has been reported to increase emergence reactions in patients treated with midazolam and ketamine (Restall et al., 1990). However, these reported effects of the two drugs combined were not formally investigated using double blind, placebo-controlled methods until Krystal et al. (1998c) examined the interactive effects of lorazepam and ketamine. In this study concomitant administration of lorazepam and ketamine reduced anxiety and depression ratings on the BPRS. It did not, however, antagonise any of ketamine's other psychotomimetic or cognitive effects. In fact, lorazepam

potentiated the amnestic and sedative actions of ketamine consistent with the anaesthesia literature (Freuchen et al., 1976). It is likely that this potentiation is at least partially responsible for the capacity of BDZs to increase the clinical tolerability of ketamine.

Ketamine is also thought to have small, yet significant effects at the DA transporter at sub-anaesthetic doses (Irufine et al., 1991). A [^{14}C]2-deoxyglucose (2-DG) uptake study in rodents demonstrated that haloperidol potentiated the uptake of 2-DG in specific brain regions associated with administration of sub-anaesthetic doses of ketamine including the medial prefrontal cortex, retrosplenial cortex, hippocampus, nucleus accumbens, basolateral amygdala and anterior ventral thalamic nucleus (Duncan et al., 2003). This finding could relate to the work of Lahti et al. (1995; 2001) discussed above, where haloperidol-treated schizophrenic patients showed greater increases in psychotic symptomatology after ketamine administration than neuroleptic free patients. Krystal et al. (1999b) also examined the interactive effects of haloperidol and ketamine in healthy volunteers. Their main finding was that haloperidol reduced ketamine-induced impairments on tasks tapping frontal functioning such as the WCST and Gorham's proverb test but did not attenuate impairments on any other tasks.

The failure of typical antipsychotic treatments to block ketamine-induced psychotic symptoms provoked an investigation into the effectiveness of novel antipsychotic treatments in altering NMDA-R induced psychotomimetic effects. Clozapine is one such 'atypical' antipsychotic treatment that has proved effective even in patients resistant to typical antipsychotic treatment such as haloperidol. The neurochemical action of clozapine is not entirely clear but it is known to have some affinity for dopamine receptors (D_1, D_2, D_3, D_4), serotonin receptors (5-HT_2, 5-HT_3, 5-HT_6, 5-HT_7), muscarinic cholinergic and adrenergic receptors (α_1 , α_2). Clozapine, but not drugs such as haloperidol, has also been shown to affect glutamatergic neurotransmission. Preclinically clozapine increases glutamate levels in the PFC (Daly & Moghaddam, 1993)and stimulates glutamate release from the nucleus accumbens (Yamamoto & Cooperman, 1994) . Clozapine is also reported to be the most effective antipsychotic in combating the cerebrocortical neurotoxicity caused by NMDA-R

antagonists (Olney & Farber, 1994). In rodent models clozapine, unlike typical antipsychotic drugs or D_2, D_1, and 5-HT_2 antagonists, has been shown to prevent the effects of NMDA-antagonists on PPI (Bakshi et al., 1994).

The ability of clozapine to blunt ketamine-induced psychosis in a population of schizophrenic patients was reported by Malhotra et al. (1997a). Patients were antipsychotic drug free and then underwent a single challenge with one ketamine dose and a placebo. They were then treated with clozapine and participated in another ketamine challenge (except one patient who was tested on clozapine first). Ketamine challenge alone increased rating of thought disturbance and withdrawal-retardation. Clozapine treatment significantly blocked the ketamine-induced thought disturbance, however these results are complicated by the lack of randomisation of treatment order.

Much of the research described in this section has been concerned with formally testing drugs with a known clinical efficacy for the treatment of schizophrenia or ketamine induced phenomena. However, an eventual aim of developing a model of the symptoms of schizophrenia is to suggest new potential antipsychotic drugs. No licensed antipsychotic drug to date has been developed with the aim of modulating NMDA-R or glutamatergic function. Considerable debate in the field has centred around whether a hypo- or hyper-glutamatergic model of schizophrenia is indicated by the literature. As previously mentioned, preclinical microdialysis research would now suggest that the effects of NMDA-R antagonists are mediated by increased glutamate release in the PFC (Adams & Moghaddam, 1998; Moghaddam et al., 1997). This would suggest that the neuropsychiatric effects of ketamine are mediated not by attenuation of glutamate activity at the NMDA-receptor but by increased glutamate activity at non-NMDA glutamate receptors. This concurs with mounting evidence from post-mortem studies related to hyperglutamatergic functioning in schizophrenic brains, including an overabundance of glutamatergic synapses in the frontal cortex (Deakin & Simpson, 1997). The hyperfunction hypothesis was tested in a study using the metabotropic type II glutamate agonist LY3540740. The compound decreased the cognitive and motor effects of PCP in rats (Moghaddam et al., 1997). Moreover, the same compound attenuated ketamine-induced working memory deficits in humans (Krystal et al., 2005). In addition, a study with healthy volunteers investigated the interactive effects of

ketamine and lamotrigine (Anand et al., 2000). In this study lamotrigine was found to decrease the ketamine-induced positive and negative symptoms of schizophrenia as indexed by the BPRS, as well as attenuating ketamine induced perceptual distortions and impairments on the Hopkins verbal learning test. Taken together, the above evidence would seem to suggest a role for hyperglutamatergic functioning in the neuropsychiatric effects of ketamine and other NMDA-R anatgonists and possibly in some of the symptoms of schizophrenia.

1.10.7. Summary of acute psychotomimetic effects

Studies that have used NMDA-R antagonists to induce schizophrenic symptoms in healthy volunteers have consistently found increases in ratings on the BPRS and other scales of psychotic symptoms e.g. the Scale for the Assessment of Negative Symptoms (SANS) and the Scale for the Assessment of Thought, Language and Communication (TLC). The exact pattern of symptoms has varied. The only consistent symptoms that have been induced across healthy volunteers are conceptual disorganisation and thought disorder. These differences probably reflect an insensitivity of the BPRS in measuring drug-induced symptoms and differences in dose. There may be difficulties administering the BPRS to very withdrawn ketamine participants. Studies that have attempted to relate cognitive symptoms to psychotic symptoms have yielded no clear results to date.

Symptom provocation studies that have administered ketamine to patients have again only reliably yielded changes on the thought disorder factor and conceptual disorganisation item of the BPRS. However, the common thread from the patient research is that ketamine, when administered to people with schizophrenia, induces symptoms similar to their own acute-phase symptoms, e.g. delusions of the same nature, auditory hallucinations of the same voice. This is certainly encouraging for the NMDA-R hypofunction model of schizophrenia in that other pharmacological models of schizophrenia (e.g. d-amphetamine), induce homogenous symptoms (Lieberman et al., 1987). The ability of ketamine to induce negative symptoms in schizophrenic populations appears to still be in dispute, which may be a function of the different populations and drug regimes used or may reflect underlying neurobiological differences in glutamatergic function.

Studies have varied as a function of the particular anti-psychotic drugs patients were administered. In an attempt to resolve this issue and elucidate the effects of ketamine on the various neurotransmitter systems, the interactive effects of NMDA-R antagonists and several pharmacological agents have begun to be investigated. Findings have been complicated by several issues. Firstly, the sedative effects of these drugs (e.g. haloperidol, lorazepam) make it difficult to measure their effects on reducing ketamine-induced symptoms. It is possible that drugs such as lorazepam and haloperidol may be effective at attenuating ketamine-induced psychosis in higher doses that are unfeasible due to sedative effects. Order effects in the patient studies, given the tachyphylaxis (rapid tolerance) associated with ketamine have also complicated interpretation of results. The interactive effects of ketamine and other drugs would seem to suggest a DA modulation of executive frontal impairments induced by ketamine and a role of hyperglutamatergic activity in the psychotomimetic and episodic memory effects of ketamine. The exact mechanism of these effects and the precise alleviation of impairment needs to be investigated further as does ketamine's impact on other NT systems (e.g. NA and opiod).

Often, psychopharmacological models have yielded important insights into the pathophysiology of schizophrenia. For instance the discovery of stimulant psychoses was one of the key factors in developing the influential DA model of schizophrenia. The weight of evidence that has emerged from the investigation of NMDA-R antagonism behaviourally and neurologically indicates a role of hyperglutamatergic functioning in schizophrenia. In order for the model to persist it should inform knowledge about the neurobiology of schizophrenia. Whilst this is beyond the scope of this review, recent post-mortem data has begun to demonstrate NMDA-R abnormalities in the schizophrenic brain (Krystal et al., 2000a) and this further contributes to the validity of NMDA-R hypofunction as a model of some of the symptoms of schizophrenia.

PART III: CHRONIC EFFECTS OF NMDA-R ANTAGONISTS

1.11.1 NMDA-R antagonist associated neurotoxicity studies

It is now widely accepted that high synaptic glutamate concentrations are neurotoxic and that in conditions such as ischaemia, hippocampal glutamate levels increase markedly. This 'excitotoxicity' as discussed in Section 1.4 can be attenuated with NMDA-R antagonists. However, several animal studies have demonstrated that NMDA-R antagonists can themselves induce neurotoxicity after very high acute doses or chronic exposure (Olney et al., 1989; Olney et al., 1991) . Olney et al. (1989) demonstrated that ketamine, PCP and MK-801 can all induce neurotoxic effects in rats. The degree of potency of neurotoxic effects (MK-801> PCP> ketamine) suggested that non-competitive NMDA-R antagonism was responsible. They observed a vacuolisation of neuronal cytoplasm in the posterior cingulate cortex (retrosplenial cortex). Whilst this vacuolisation gradually disappeared 12-18 hours after the drug was administered, later research demonstrated that a higher dose of MK-801 resulted in cell death could still be observed 48 hours after drug administration (Allen & Iverson, 1990) and irreversible vacuolisation after PCP in the pyramidal cells of the hippocampus has also been observed (Gao et al., 1993).

Furthermore, repeated administration of PCP or MK-801 generates neurotoxicity in the dentate gyrus and olfactory regions, parahippocampal and hippocampal regions and the retrosplenial, cingulate and entorhinal cortices (Corso et al., 1997; Ellison & Switzer, 1993; Ellison, 1995; Horvath & Buzsaki, 1993), predictably these are areas with dense populations of NMDA-Rs. More recently, research into the effects of repeated ketamine administration has suggested that its chronic effects are observable however less profound. Repeated ketamine leads to increased neurogenesis in the sub-granular region of the hippocampus (Keilhoff et al., 2004b) but also decreased immunoreactivity of parvalbumin in GABA-ergic interneurons in the hippocampus. In addition, decrease c-Fos binding in the dentate gyrus of rats has been observed following repeated ketamine application compared to controls (Keilhoff et al., 2004a). This may reflect a reduced ability of the hippocampus to cope with novelty and complexity in stimuli. Other effects observed in rats following repeated ketamine were increased D2 binding in the

hippocampus and decreased Glu binding in the frontal cortex (Bernstein et al., 2003). Collectively these findings are interesting in that they are fairly consistent with neurological differences observed in schizophrenia in post-mortem studies (Tsai et al., 1995; Reynolds & Beaseley, 2001).

Several studies have examined the reversibility of NMDA-R antagonist-induced neurotoxicity. Olney et al. (1991) found that the vacuolisation produced by MK-801 was blocked by GABA-ergic drugs (diazepam and barbiturates) and anticholinergic drugs (scopolamine, benzotropine, trihexylphenidyl). Olney et al. (1991) suggested that the effectiveness of these drugs was attributable to a circuit in which cholinergic input to these neurons was normally modulated by inhibitory GABA cells, which were normally excited by NMDA-R mediated glutamate input. Other research has also demonstrated compounds to be effective in preventing ketamine induced neurotoxicity in animals. These include haloperidol (Nakki et al., 1996), clozapine and olanzapine (Farber et al., 1996) , halothane (Nakao et al., 1996) and agonists of the 5-HT_{2A} receptor (Farber et al., 1998). Olney et al. (1999) have suggested that the neurotoxic properties of the NMDA-R antagonists may be analogous to processes operating in schizophrenia. Unfortunately for this theory, many of the drugs that prevent neurotoxicity in animals do not diminish the psychotomimetic effects of ketamine in humans. Moreover some of these drugs e.g. 5-HT_{2A} agonists such as the indoleamines, LSD and psylocibin, are in fact themselves psychotomimetic.

The neuronal vacuolisation described in some of the above studies has interesting age and sex dependent profiles. Following MK-801 or PCP, female rats were more vulnerable to neuronal vacuolisation in the retrosplenial cortex than adult male rats (Olney et al., 1989). Whilst these results have been replicated in mice (Akinci & Johnston, 1993), it is not clear the extent to which these changes hold for higher species. MK-801 additionally induces no vacuolisation in female rats aged 1 month, weak vacuolisation in rats aged 2-months but clear vacuolisation in 3 month-old rats (Fix et al., 1994; Farber et al., 1995; Fix et al., 1993). Heat-shock protein 70 gene induction following ketamine, PCP and MK-801 administration was also found to have a similar age dependent profile (Sharp et al., 1992). Whilst the density of NMDA-Rs changes with age, the age-dependent neurotoxic effects do not fit this pattern. However

these studies have only been conducted in female rats and thus these effects could conceivably be due to hormonal effects linked with sexual maturation (Ellison, 1995). It is tempting to draw parallels between the age-related onset of NMDA-R antagonist effects, which is also manifest in human emergence reactions, and the age related onset of schizophrenia. However, the human evidence for an age-dependent profile of emergence phenomena is scant and indeed anecdotal evidence suggests recurrent hallucinations in children administered ketamine as an anaesthetic (Perel & Davidson, 1976).

1.11.2. Studies of the behavioural and cognitive effects of chronic NMDA-R antagonists in animals

Although such studies are few, initial evidence suggests chronic administration of NMDA-R antagonists results in a different, more selective profile of deficits than acute exposure. Both chronic PCP (Sams-Dodd, 1995, 1996; Steinpreis et al., 1994) and ketamine (Bernstein et al., 2003; Keilhoff et al., 2004b) leads to decreased social interaction in rats. Jentsch et al. (1997b) investigated the effects of subchronic administration of PCP on a spatial delayed alternation task in rats. Impairments were seen at long delays but not after no delay, implying a working memory deficit. Chronic PCP exposure in monkeys also produced deficits on a response inhibition task (Jenstch et al., 2000). The executive functions investigated in these two studies have been linked to PFC. Thus the preliminary results in this field suggest that this region may mediate the deficits induced by chronic PCP (the dorsolateral PFC in monkeys and the medial PFC in rats). Chronic PCP exposure has also been reported to reduce frontal lobe glucose utilisation in humans as discussed in section 1.1.3. (Wu et al., 1991). On the basis of the selectivity of these deficits and evidence from PCP users, it has been suggested that chronic administration of NMDA-R antagonists may provide a better model of schizophrenia than acute antagonism (Jentsch & Roth, 1999).

1.11.3 Chronic behavioural and cognitive effects of NMDA-R antagonists in humans

Evidence for the chronic effects of ketamine and PCP in humans comes solely from abusing populations and is hence subject to the many limitations of naturalistic drug research (e.g. poly-drug use, pre-existing population differences). In one of the few published studies of the cognitive effects of chronic PCP, Carlin et al. (1979) administered the Halstead-Reitan neuropsychological battery to 12 PCP abusers, 12 poly-drug users and 12 non-drug controls. This study found the poly-drug group and the PCP group could not be differentiated from each other and both were impaired relative to controls on this scale. Ware (1979) compared 8 hospitalised PCP users to 8 poly-drug users on the WAIS-R and the Halstead Reitan. Differences were observed on the WAIS-R but not the Halstead- Reitan. Cognitive impairments were found in a more recent study (Cosgrove & Newell, 1991) in a group of 15 chronic PCP drug users. They found an overall impairment on a range of cognitive tasks (verbal fluency, trailmaking, verbal memory, digit symbol substitution, block design). In this study the PCP abusers ceased use of the drug for 4 weeks and then were retested. Verbal memory scores were found to improve on cessation of PCP use along with trailmaking and digit symbol substitution.

Surveys of PCP users contain numerous reports of persistent problems with memory, speech and thinking (Fauman & Fauman, 1978). An early survey of ketamine users also indicated the perceived cognitive effects of long-term use to be attentional dysfunction and decreased sociability (Siegel, 1978). Feldman et al. (1980) described the chronic effects of PCP as leading to significant cognitive impairment characterised by confusion, thought disorder and severe memory loss referred to as 'burnout' by users. A single case report in the literature also indicates chronic memory impairments as a result of ketamine use (Jansen, 1990).

Repeated doses of PCP in abusing populations have also been found to induce persistent schizophrenia-like symptoms such as psychosis, auditory hallucinations, blunted affect, cognitive dysfunction and social withdrawal (Allen & Young, 1978; Javitt & Zukin, 1991; Rainey & Crowder, 1974). Unfortunately, the majority of these

reports are based on case studies or small sample case-control studies. Anecdotal reports of psychosis following ketamine abuse also exist (Lilly, 1978; Moore & Altounian, 1978). One large study of 1000 patients presenting with acute PCP intoxication found that 25% developed catatonic or psychotic reactions following resolution of the acute brain state (Allen & Young, 1978).

Recently, two studies examined the acute and residual behavioural and cognitive effects of ketamine in recreational users. Curran & Morgan (2000) compared ketamine abusers with polydrug using controls. Participants were assessed on the night of their drug use and then 3 days later on tests tapping a several memory functions, attention, mood dissociation, and schizoptypal symptomatology. Acutely, the drug users were impaired in a similar pattern to laboratory studies of sub-acute effects discussed above (e.g. Krystal et al., 1994). Three days later the recreational users were still significantly impaired on tests tapping semantic and episodic memory and had elevated scores compared to controls on schizotypal and dissociative symptoms scales. A similar procedure was used by Curran & Monaghan (2001) who compared frequent ketamine users with infrequent ketamine users to explore whether the residual memory effects were as a result of chronic ketamine use or pre-existing differences in people attracted to ketamine abuse. The acute effects were similar between the frequent and infrequent users, despite higher doses taken in the frequent users, indicating some degree of tolerance to the cognitive impairments associated with ketamine administration. Three days after use of the drug the frequent users still exhibited impairments in tasks tapping episodic and semantic memory, whereas the infrequent users did not. These memory impairments were not as profound in the infrequent users, suggesting they were not a result of residual impairments following a single dose. Rather they appear to be cumulative, and a function of degree of ketamine abuse. The profile of cognitive impairments observed with these recreational users, especially in episodic and semantic memory, is akin to aspects of the profile of impairment in schizophrenia. Naturalistic studies such as these are difficult to relate to models of schizophrenia, as it is not clear whether the cognitive impairments observed here, and brain activation differences, reflect a predisposition to psychosis in this population. Furthermore, ketamine is frequently abused with a variety of other drugs such that the effects that are attributable to ketamine are difficult to tease apart. However using samples that compare within

populations of ketamine users, or that use poly-drug using controls, can help address some of these potential difficulties.

1.11.4 PCP, ketamine and dependence

" *I'd estimate that more than half of those who have tried and liked K have become involved in the trap of repeated use...in most cases this syndrome in some way de-structures, disorganises and even threatens their lives...*"

Rameses Sputz, High Times
(1989)

PCP self-administration has been demonstrated across several species including rodents (Marquis et al., 1989), dogs (Risner, 1982) and non-human primates (Carroll, 1990). Ketamine and PCP have been shown to be equally effective as reinforcers, and are both much stronger reinforcers than dizocilpine (Winger et al., 2002). Ketamine was found to have the fastest onset of action of the arylcylohexamines (Winger et al., 1989), which is proposed to play a role in the reinforcing properties of drugs. Primates have been shown to self-administer PCP at doses that are behaviourally toxic to the animal (Balster & Woolverston, 1980) although this is not an uncommon finding amongst drugs of abuse. Many of the reinforcing properties of drugs are generally attributed to DAergic effects (Koob & Nestler, 1997) and ketamine, as discussed in section 1.1.6, has effects on this neurotransmitter system. However, it has been suggested that glutamate and the NMDA-R have also be involved in processes mediating dependence and withdrawal symptoms (Noda & Nabeshima, 2004; Weiss & Koob, 2001). From the perspective of addiction research an interesting finding observed by Krystal et al. (1997) was the failure of haloperidol to block the ketamine induced 'high' as rated on visual analogue scales. Concordant with this finding is preclinical research suggesting that the reinforcing properties of NMDA-R antagonists are not blocked by D2 receptor antagonists (Carlezon & Wise, 1996) and that glutamate may have a role to play in the neurobiobehavioural problem of drug abuse (Cornish et al., 1993).

Tolerance to, and dependence on, PCP and ketamine have been observed in animal studies of chronic drug treatment and withdrawal (Balster & Chait, 1976). Dependence

is inferred following withdrawal from chronically administered PCP, in the reduction of food intake in monkeys (Carroll & Carmona, 1991) and rodents (Wessinger & Owens, 1991), in a similar manner to that observed in stimulant dependent humans. In these studies however few physical symptoms of drug withdrawal were evident and patterns of responding suggest that the above effect may be related instead to motivational processes (Carrol & Carmona, 1991).

Very few studies have investigated the dependence forming potential of PCP or ketamine in humans. Whether ketamine and PCP are associated with physical or psychological dependence is unclear. One study of PCP users found cessation of use of the drug produced restlessness, depression and feelings of drug craving (Tenant et al., 1981). In the previously cited study of the chronic cognitive effects of PCP, Cosgrove & Newell (1991) found that of 33 patients wishing to stop their use of PCP only 15 were able over a one month period, which indicates some form of dependence.

In the ketamine literature, many anecdotal reports exist of ketamine dependence (Ahmed & Petchovsky, 1980; Hurt & Ritchie, 1994a; Jansen, 2000; Kamaya & Krishna, 1987a; Siegel, 1978) but no controlled studies have as yet been conducted. Ketamine has also been shown to alleviate withdrawal symptoms in opiate addicts (Herman et al., 1995) and part of this effect may be mediated by its own opioid effects. The degree of dependence and withdrawal caused by abuse of ketamine has still yet to be investigated.

1.11.5. Summary of Chronic Effects

Neurotoxicity research has demonstrated some evidence for lasting neuronal damage in rats following chronic, high doses of highly potent NMDA-R antagonists and more subtle, yet enduring, changes following ketamine. The generalisability of this data to human-abusing populations is limited again by doses, drugs used (e.g. primarily MK-801) but also by metabolic and structural differences in rodent and human brains. Interesting age and sex-dependent profiles of NMDA-R antagonist neurotoxic effects have been observed, with young rats showing insensitivity to NMDA-R antagonist induced neurotoxic effects and females being more sensitive than males. The age-

dependent profile invokes parallels with age dependency in schizophrenia and with onset of psychotomimetic effects of ketamine and PCP.

Preclinical research into the cognitive effects of chronic ketamine is relatively scant. The studies that have been conducted indicate persisting deficits in social interaction, working memory and response inhibition. Human research is also limited. Studies have demonstrated persisting cognitive impairments in both ketamine and PCP users, when not under the acute effects of the drug and there is some evidence of persisting psychotic effects with both drugs. In ketamine users where effects were characterised by a range of cognitive tests, the most marked cognitive impairments, when drug free, were in tasks tapping semantic and episodic memory. It is not clear from the literature whether these deficits reflect some form of neurotoxicity, outlined at the beginning of the section, or are more transient, reversible changes in receptor functioning. Despite anecdotal reports, it also unclear from the literature the extent to which tolerance of and dependence on ketamine may form. Given the increasing use of ketamine recreationally further investigation of these questions is clearly important.

1.12 Overview and Research Questions

The work presented in this chapter has reviewed studies examining the effects of NMDA-R antagonists, in particular ketamine, in humans and animals. These drugs have been investigated principally in relation to their capacity to transiently induce psychosis as they appear to produce the most convincing model of schizophrenia of any pharmacological compound. In addition, interest in these compounds has stemmed from their action as an NMDA-R antagonist, as it is at this receptor that some of the synaptic plasticity important in learning and memory has been demonstrated to occur. Research has accordingly examined the cognitive consequences of NMDA-R antagonism. A further important area of research, which has been thus far relatively neglected, is the effect of ketamine on the growing number of people who abuse this drug.

Broadly, the human research so far has demonstrated that an acute dose of ketamine produces a consistent increase in schizophrenia-like effects, both in healthy volunteers and stabilised schizophrenics. Following ketamine challenge, impairments to memory

and cognition occur but there have been some inconsistencies in the literature and a lack of through mapping of cognitive effects. Recent work has suggested the existence of chronic effects of ketamine in humans who repeatedly take the drug for the ketamine 'high'. Additionally there have been suggestions in the animal literature that chronic administration of NMDA-R antagonists may provide a better model of schizophrenia than the acute effects.

A primary aim of this research was to investigate the causes and consequences of ketamine use in drug users who repeatedly self-administer this compound. As ketamine cannot be given to healthy individuals chronically in the laboratory for ethical reasons, this population are particularly interesting in that they provide a naturalistic window onto ketamine's chronic effects. In the work presented in this thesis, I also aimed to characterise further some of the hitherto neglected or under-explored cognitive effects of an acute dose of ketamine in healthy volunteers. This was to serve two functions: it was both interesting, in its own right, to further delineate the effects of an acute dose of ketamine on specific cognitive processes, but it also was hoped it would allow for a comparison between the acute and 'chronic' effects of the drug, where possible, on the same tasks. In addition, as work suggesting chronic effects of ketamine in drug users has found deficits 3 days after use of the drug, a consequent objective was to investigate whether there were any residual (sub-acute) effects in healthy volunteers. If not, then this would suggest that any deficits observed may be chronic effects of the drug. Further, and perhaps most clinically relevant to this population of drug users, if chronic effects were observed, I intended to explore whether these were reversible on reduction or cessation of use of ketamine.

In order to examine some of the causes of repeated ketamine use, I aimed to characterise the effects of ketamine on processes that have been hypothesised to be involved in drug abuse, such as impaired response inhibition, both in ketamine users and following an acute dose of ketamine. I also aimed to tap into the degree to which the drug is subjectively reinforcing, in these two populations.

A secondary aim of this thesis was to contribute to evaluating the ketamine model of psychosis and especially the suggestion that chronic administration of the drug

produces symptoms more similar to schizophrenia than following an acute dose. Data obtained from the planned work above would contribute to this evaluation but, more specifically, I aimed to investigate processes hypothesised to underlie symptoms in schizophrenia, such as self-monitoring and gating impairments. It was hoped that this might also clarify whether glutamatergic abnormalities contributed to any of these deficits. This work in turn would expand the intended characterisation of the chronic and acute cognitive effects of ketamine.

The work presented in thesis will attempt to address the above broad aims with a series of experiments: specific aims and hypotheses are reported in each experimental chapter. A total of three acute administration of ketamine studies were conducted in this thesis. As such data on the same participants are reported in different chapters: Chapter 2 reports data collected in the same study as that in Chapter 6; the acute ketamine data for the Go/No-go task reported in Chapter 7 was collected in the same study as the acute ketamine semantic priming data reported in Chapter 4. Order of test administration is given in Appendix 1.

Chapter 2: Ketamine and Memory Systems

Acute effects of ketamine on memory systems and psychotic symptoms in healthy volunteers

"One problem I find with Ketamine is that the experience is difficult to bring back and reintegrate with routine reality. Memory of the experience is even difficult. Within hours after coming back, 99% of the experience is inaccessible to my current conscious mind. The Ketamine experience is so bizarre and otherworldly that a normal mind can't even conceive of experiencing in this manner. It feels as though some part of the mind protectively closes off access to the dimensions experienced on Ketamine..."

D.M.Turner, The Essential Psychededlic Guide, 1994

2.1 Overview

N-methyl-d-aspartate (NMDA) receptor antagonists have been demonstrated to induce schizophrenia-like symptoms and cognitive impairment in humans. The NMDA receptor has been strongly implicated in memory, but research to date on the effects of NMDA-antagonists has examined only some aspects of human memory functions. This study used a double-blind, placebo-controlled, independent groups design with 54 healthy volunteers to examine the effects of infusions of two doses (0.4, 0.8 mg kg^{-1}) of the NMDA antagonist ketamine upon the five human memory systems (Tulving, 1985), aspects of executive functioning and schizophrenia-like and dissociative symptoms. Ketamine produced a dose dependent impairment to episodic and working memory and a slowing of semantic processing. Ketamine also impaired recognition memory and procedural learning. Attention, perceptual priming and executive functioning were not affected following the drug. In addition, ketamine induced schizophrenia-like and dissociative symptoms which were not correlated with the cognitive measures. These data suggest that, in humans, ketamine produces a selective pattern of impairments to working, episodic and procedural memory but not to perceptual priming, attention and aspects of executive functioning.

2.2 Introduction

The five memory systems proposed by Tulving (1985; Tulving & Schacter, 1994) were outlined in the previous chapter (Section 1.9.2). Previous research has addressed the effect of NMDA antagonism, via administration of ketamine, on some of these human memory systems. Whilst several studies have found ketamine induced impairments in verbal memory (e.g. Krystal et al., 1994; Harborne et al., 1996; Malhotra *et* al., *1996*), only one study has investigated the effect of NMDA-receptor antagonism on the episodic memory system (Hetem et al., 2000; *subsequent to writing, Honey et al., submitted*). Both 'remember' and 'know' responses were reduced following a single dose of ketamine when compared to placebo. The authors argue that this indicates an impairment of episodic memory. A reduction in 'remember' responses supports this assertion but the reduction in 'know' responses may reflect semantic impairments. However, the lack of 'lures' in this study complicates interpretation of the findings. The effect of ketamine on the semantic memory system has been investigated in tasks in which participants are required to generate category members (semantic fluency) or words beginning with a specified letter (phonemic fluency). Conflicting results have been obtained from ketamine studies with fluency tasks of both impaired (Adler et al., 1998) and preserved (Ghoneim et al., 1985) category fluency, and similar findings of an impairment to verbal fluency in some (Adler et al., 1998; Krystal et al., 1998c) but not all (Krystal et al., 1999a) studies. Findings concerning ketamine's effects on working memory are also conflicting. Impairments have been found on the N-back task (Adler et al., 1998) but not on a spatial working memory task (Newcomer et al., 1999). In addition, two studies have found preserved backwards digit span (Ghoneim et al., 1985; Harris et al., 1975) but one study has found impaired forwards digit span (Harris et al., 1975). Newcomer & Krystal (2001) in their review of memory research with NMDA-antagonists, noted that ketamine's effects on memory and learning appear to be preferential to their effects on other cognitive functions and may be dose dependent. However, the effects of ketamine on the other two memory systems, procedural learning and perceptual representation have not previously been investigated.

Although several studies have investigated the acute cognitive effects of ketamine on memory, they have been confined to single doses or, where more doses have been used, crossover designs have complicated interpretation of results due to the tachyphylaxis (or rapidly developing tolerance) that occurs following ketamine administration. Further, previous research has not examined the effect of this drug on the full range of human memory functions.

Therefore, the present study aimed to thoroughly characterize the dose-response impact of ketamine administration on the different memory systems. It was hypothesized that ketamine administration would impair episodic and working memory, replicating and extending previous findings. By using a more specific semantic memory task, this study hoped to clarify the effect of ketamine on this memory system. No prediction could be made as to the effects of ketamine on procedural learning or perceptual priming as these have not previously been investigated. The subjective effects that ketamine was expected to induce were increases in dissociative and schizotypal symptomatology.

2.3 Methods

2.3.1 Participants and Design

Participants were recruited through an advertisement and were paid for their participation. The study was carried out in accordance with the Declaration of Helsinki and was approved by the institutional ethics committee (the UCL/UCLH Committee on the Ethics of Human Research). All participants gave written, witnessed, informed consent. Inclusion criteria were that participants were between 18 and 35 years old and native English speakers. Participants were then selected for participation by a screening interview to exclude individuals with a propensity towards psychiatric disorders, and any substance misuse or general health problems.

Volunteers were screened by semi-structured interview (conducted by CM), questionnaire and physical examination to exclude those with i) psychotic illness in a

first-degree relative; ii) current or past psychiatric problems [> 18 on the Beck Depression Inventory, (Beck, 1978) and >54 on the Speilberger Trait Anxiety Inventory (Spielberger, 1983) were used to screen current psychopathology in addition to DSM IV diagnostic criteria for psychotic illnesses iv) any significant history of substance misuse, including prior ketamine use; v) a positive result in a urinalysis screening for drugs of abuse; vi) hypertension; vii) outside normal levels (>25) on the Body Mass Index viii) a known allergy to ketamine; ix) those currently taking any prescribed medication (excluding oral contraceptives) x) any general physical health problems. At the screening interview, the premorbid IQ of each participant was also assessed by the 'Spot the Word' test (Baddeley et al., 1993), an estimate of verbal intelligence based on lexical decision; trait dissociation was assessed by the Dissociative Experiences Scale (DES – (Bernstein & Putnam, 1986).

Sixty-nine volunteers responded to the advertisement and eleven were excluded for failing to meet inclusion criteria (history of mental illness - 2, family history of mental illness - 3, prior substance misuse – 3, currently on medication - 3). 58 healthy volunteers took part in this study. Of these, four participants dropped out: two had adverse reactions to cannulation, one had an adverse reaction to 0.8mg kg^{-1} ketamine and did not wish to continue with the experiment, and one participant was excluded due to failing a urine screen upon the follow-up testing day. In total 54 participants completed the study (mean age 22.53±3.52 years). A mixed model, independent group design was used in which male and female participants were randomly allocated to treatment with either 0.8mg kg^{-1} ketamine hydrochloride, 0.4 mg kg^{-1} ketamine hydrochloride or placebo. Groups were balanced for gender; with 9 females and 9 males in each group. Double-blind procedures were used throughout. Test versions were counterbalanced across participants and design.

2.3.2 Drug Administration

Participants received either ketamine (0.4 mg kg $^{-1}$ or 0.8 mg kg $^{-1}$) or saline placebo (0.9% NaCl) intravenously for 80 minutes. Pilot work demonstrated that tasks were sensitive to these doses of ketamine. A bolus dose was not used to minimise adverse effects. Low doses were chosen to ensure participants would understand the instructions to the tasks. This dosing regimen produces a dose of 0.005mg/kg/min or 0.01 mg/kg/min ketamine in the low and high dose groups which is comparable to those used in previous studies (e.g. Krystal et al., 1994; Adler et al., 1998). Using local anesthesia, a 16 gauge intravenous cannula was inserted in the non-dominant forearm and after 5 minutes the ketamine infusion began via a Graseby intravenous infusion pump. A loading dose was used in order to minimize adverse effects. A urine sample was taken before the infusion began and a peripheral venous blood sample was taken 65 minutes after commencing the infusion. Plasma was obtained immediately from blood samples by centrifugation and samples were stored at -80°C. Ketamine levels were measured using gas chromatography (ABS Laboratories, National Poisons Unit, London).

2.3.3 Procedure

Testing occurred at either 9am or 1 pm and the time of testing was broadly matched across groups. Participants arrived at the hospital after completing an overnight fast for morning testing, or a minimum of six hours fasting for afternoon testing. Participants were assessed on the pre-drug battery for 35 minutes. They were then allowed to rest for 15 minutes and then were cannulated. Approximately 5 minutes after cannulation, the anesthetist began the infusion. Participants were tested on a battery of tests similar to the pre-drug battery beginning 20 minutes after the start of infusion. Throughout the 80 minute infusion the participant's pulse, blood pressure and electrocardiagram were monitored. After infusion participants were provided with light refreshments and were then assessed 30 minutes later and then at hourly intervals by the medical staff as to their 'street readiness'. A follow-up battery was given 3 days after the acute dose, findings of which are reported elsewhere (Chapter 6).

2.3.4 Assessments

Tests were selected to assess the range of human memory functions, dissociative and psychotogenic symptoms and mood effects. Tests were administered in the following order: subjective drowsiness, speed of comprehension, serial reaction time task, trailmaking, word-stem completion and cued recall, N-back working memory task, source memory, CADDS SSQ, subjective drowsiness.

Cognitive Tasks

Speed of Comprehension (Baddeley et al., 1992) : One of the factors tapped by this task is semantic memory. Participants were presented with 200 sentences some of which made sense (e.g. 'Sharks are good swimmers') and some of which do not (e.g. 'Wives are made in factories'). They were given two minutes to mark which sentences made sense and which ones did not. The task was scored in number of sentences completed and number of errors.

Source Memory Task (Wilding and Rugg, 1996): This task was chosen as an index of episodic memory, i.e. awareness of when and where a stimulus was encoded. Stimuli consisted of 240 low frequency words. The words were divided randomly into six study lists of 40 words. In each study list half the words were spoken in a female voice and half in a male voice (allocation was randomly determined). At study words were presented to participants aurally, played on a tape recorder. During the study phase participants listened to each word, repeated it aloud and then, depending upon the gender of the voice it was presented in, rated the word as either 'pleasant/ unpleasant' or 'abstract/ concrete'. After completing the list, there was a delay of six minutes, filled with another task, and then participants were presented with a test list. Test lists were created by combining the study list with another study list that had not been presented. Test words were presented visually on a computer monitor. Participants were instructed to say aloud whether each word was one that they had heard before and if so, whether it had been presented in a male or female voice. Participants gave their responses

verbally. Word recognition responses were recorded as hits, false alarms, misses and correct rejections. Source errors were also recorded. Preliminary analysis showed no group differences across the two encoding conditions so data were collapsed.

Word stem completion and cued recall (Bishop & Curran, 1995): This task was chosen as an index of perceptual priming and free recall, using a 'Levels of Processing' (LOP) encoding task (to distinguish between the perceptual representation system, which should not be affected by LOP, and the episodic memory system which should be affected by LOP). Stimuli were 96 words. In the study phase the participants were required to read aloud 64 words presented on the computer screen each for 4000ms with a 1500ms interval. For each block of 32 words the participants were given encoding instructions. For the semantic encoding condition participants were instructed to say whether the word presented depicted something living or non-living. For the physical encoding condition participants were instructed to say how many vowels were in each of the words. Encoding condition was counterbalanced across treatment groups. In the test phase, the word-stem completion task was given before the cued recall. In the word stem completion task participants were presented with 64 word stems (16 previously semantically encoded, 16 previously physically encoded, 32 unseen) and asked to complete them with the first word that 'popped into their head' excluding proper nouns. Afterwards participants were asked if they noticed anything about the words that they had completed the word-stems with. The cued recall task then followed. Participants were given a sheet of 32 word-stems (16 semantically encoded, 16 physically encoded) and were told that they had previously been shown all of the words that completed the word-stems. Participants were then asked to complete the stems with words they remembered being shown on the computer screen. Scores were recorded in terms of completion rates across the two encoding conditions and errors in the cued recall task and non-completed stems in the word-stem completion.

N-back working memory task (Braver et al., 1997): The task used a sequential letter paradigm and manipulated working memory load incrementally. The '0-back'

condition was taken as an index of attention and the '1-back' and '2-back' conditions as tapping working memory. Stimuli were sequences of lower case consonants presented centrally for 1200ms with a 500ms inter-stimulus interval. Stimuli were organized in a pseudorandom sequence with targets occurring on 33% of the trials. Blocks were of 112 seconds (66 stimuli) each participant experienced one block in each condition at each time point (total 9 blocks). Participants were presented stimuli on a VDU and responded to stimuli with their dominant hand, pressing a 'yes' button for targets and a 'no' button for non-targets. In the '0-back' condition participants were required to respond 'yes' if they saw a target letter (e.g. M). In the 1-back condition participants responded 'yes' to a letter if it was the same as the letter before it, in the 2-back condition if a letter was the same as two before it. RT's and responses were recorded for each trial using Visual Basic software.

Trailmaking (Reitan, 1958): This task consisted of two parts, the first tapping psychomotor speed and the second executive functioning. In Part A of the task participants were required to connect 25 circles in ascending order as rapidly and accurately as possible. Part B again contains circles but with both numbers and letters in ascending order. Participants are again required to connect the circles as rapidly as possible this time alternating between the two different sequences (1 to A, A to 2, 2 to B, B to 3 etc.). A difference score was computed by taking time to complete on Part A away from time on Part B to give a measure of executive functioning controlling for simple psychomotor speed. Errors were also recorded.

Serial Reaction Time Task (SRT) (Shanks & Perruchet, 2002): This task was used as an index of procedural learning using a repeating sequence. Participants were required to press a key as soon as they see a target appear in one of four boxes on the computer screen. Participants are told that the task is a simple reaction time experiment but actually the targets appear in boxes in a set sequence, for 85% of the trials. The task thus taps participants' ability to learn this underlying sequence. After a practice block of 10 trials with no underlying sequence, participants were subjected to one of two sequences balanced across conditions, for three blocks of 100 trials (a total of 300

trials). In each trial a target (a 'X') appeared in one of the boxes. On 85% of the trials in each block the 'X' would be a location corespondent to the sequence that the participant was being trained on (probable trial). However, on 15% of the trials in each block the 'X' would appear in a location erroneous to the underlying sequence (improbable trial). The order of occurrence of the improbable trials was randomly determined. A trial ended when the participant pressed the correct corresponding key whereupon the target moved to a new location. Reaction times were recorded with Visual Basic software, and scored in terms of latency of responding correctly for probable trials, latency of responding correctly for improbable trials, number of errors on probable trials, number of errors on improbable trials.

Subjective ratings

Schizotypal Symptomatology Questionnaire (Curran & Morgan, 2000): a 30 item questionnaire designed to assess state schizophrenic-like symptoms in normal populations.

Adapted Dissociative States Scale (from Bremner et al., 1998): a 19-item subjectively rated measure tapped state dissociative symptoms.

Mood Rating Scale (Bond & Lader, 1974) : a 16-item visual analogue scale (VAS) was used to investigate subjective drowsiness.

At the end of the main session, the effectiveness of blinding was also assessed by both participant and experimenter guessing whether they thought that a drug had been administered.

2.3.5 Statistical Analyses

All statistical analyses were performed using SPSS Version 9.0. Group differences were examined using one-way ANOVAs and, where data was non-parametric, the Kruskall-Wallis test. The recognition memory component of the source memory task and the N-back were analyzed using signal detection theory (Snodgrass & Corwin, 1988). This method was selected as it allows a separation of the response bias

component from discriminability and yields a measure of not only of the ability to recognise a word/number but also the bias in responding. Within psychopharmacological research response bias can be an issue, either in terms of disinhibition or over-inhibition. Thus it is important to separate response bias, where possible, from memory data. The recognition and N-back data were then, along with most other cognitive tasks and subjective effects, analysed using 3 x 2 repeated measures analyses of variance (RMANOVA) with time (pre-drug, post-drug) as the within-subject factor and drug condition (placebo, 0.4mg kg $^{-1}$ ketamine, 0.8 mg kg^{-1} ketamine) as the between subject factor. Where significant interactions were found orthogonal contrasts were conducted comparing 1) placebo with both drug groups and then 2) low dose and high dose ketamine. Dunnett's t and simple effects were analyzed in RMANOVAS with more than two factors. Bonferroni corrections were used to control for multiple comparisons and correlations. Non-significant main effects and interactions are not reported.

2.4 Results

2.4.1 Trait Scores, Demographics and Drug dosage

There were no significant group differences in age. Participants were additionally matched in premorbid I.Q. (spot the word) test, depression, alcohol and tobacco use and trait dissociation. There were no differences in the milliliters (mls) infused for the three groups [$F(2, 51) = 0.39$ $p=0.68$] or between the weights of the groups [$F(2,51) = 0.44$ $p=0.65$] (Table 1). In total the 0.8 mg kg $^{-1}$ and 0.4 mg kg $^{-1}$ groups received a mean of 56.45± 9.19 mg and 26.74 ± 7.56 mg ketamine respectively over 80 min.

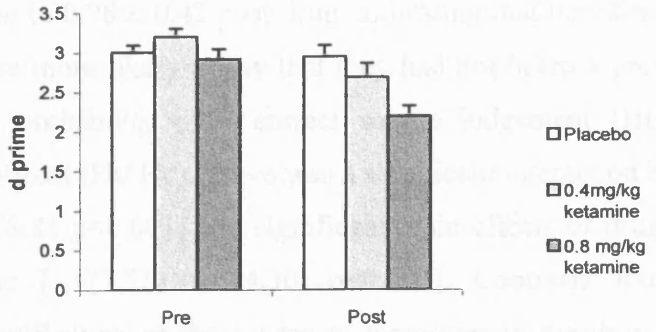
	Placebo, mean (s.d)	0.4 mg kg^{-1} ketamine, mean (s.d)	0.8 mg kg^{-1} ketamine, mean (s.d)
Age	21.83 (3.15)	21.17 (1.69)	24.17 (4.53)
Spot the word test score	50.00 (3.20)	49.67 (3.65)	49.65 (3.87)
Alcohol use, units/week	14.22 (8.89)	11.83 (7.67)	13.61 (8.51)
Tobacco use, cigarettes /day	2.11 (4.43)	3.33 (4.85)	1.78 (4.77)
BDI score	3.0 (3.6)	4.3 (4.9)	3.5 (4.9)
STA score	34.6 (10.8)	32.5 (8.79)	33.8 (9.7)
DES score	32.3 (32.39)	31.6 (30.3)	31.5 (35.5)
Weight, kg	71.29 (13.92)	66.84 (18.87)	70.56 (11.49)
mls infused	31.2 (6.05)	29.8 (3.71)	30.9 (5.58)

Table 2.1: Demographics across treatment groups

2.4.2 Cognitive Tasks

2.4.2.1 Source Memory: For recognition memory data d', an index of discriminability, and C, a measure of bias, were calculated using signal detection theory. RMANOVA analysis of discrimination (d') revealed a significant drug x time interaction [$F = (2, 51) = 8.74$ $p<0.001$] and significant main effects of time [$F(1, 51) = 42.59$ $p<0.001$] and drug [$F(2,51) = 3.84$ $p<0.05$]. (See Figure 2.1a). Contrasts revealed significantly lower

a



b

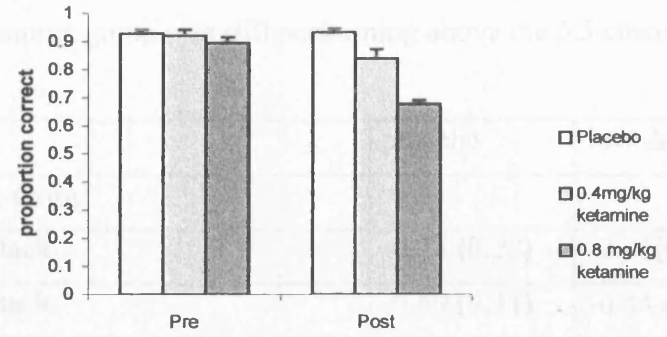


Figure 2.1a: Mean d′ index for recognition memory at each assessment point by each treatment condition; 2.1b: Mean proportion of correct source memory judgements pre and post drug across each condition

recognition memory scores in the drug groups as compared to placebo [$t(51) = 3.98$ $p<0.001$].

Analysis of the criterion (C), found a significant time x drug interaction [$F(2, 51) = 3.75$ $p<0.03$] and a main effect of time [$F(1, 51) = 21.92$ $p<0.001$]. Contrasts revealed a difference in bias between the high and 0.4 mg kg^{-1} ketamine groups, such that the

low dose group was significantly less conservative than the higher dose group [t(51)= -2.09 p<0.04]. The criterion only changed in the high dose group from 0.40 ± 0.22 pre-drug to 0.78 ± 0.42 post-drug, indicating that they became more conservative, i.e. they were more likely to say that they had not heard a previously presented word. Data on the probability of a correct source judgement (Ht) given recognition (Ht') were analyzed (Ht/ Ht'). There was a significant interaction between time and drug [F (2, 51) = 18.84 p<0.001] and significant main effects of drug [F(2,51) = 11.72 p<0.001] and time [F(1,51) = 44.30, p<0.001]. Contrasts found significantly lower correct identification of the source of memories in the drug groups as compared to placebo [t(51) = 4.91 p<0.001] and in the 0.8 mg kg^{-1} group compared to the 0.4 mg kg^{-1} ketamine group [t(51) = 3.68 p=0.001].The clear dose response relationship can be seen in Figure 1b. However even given the marked impairments of the high dose group compared to the low dose and placebo groups, it is noteworthy that the high dose ketamine group was still performing above the 0.5 chance level.

	placebo	low dose	high dose
Pre-Drug			
0-Back	-0.37 (0.28)	-0.31(0.22)	-0.37 (0.25)
1-Back	-0.49 (0.31)	-0.44 (0.33)	-0.42 (0.29)
2-Back	-0.57 (0.20)	-0.72 (0.27)	-0.65 (0.21)
Item Recognition	0.52 (0.28)	0.39 (0.24)	0.40 (0.22)
Post Drug			
0-Back	0.76 (0.29)	0.62 (0.22)	0.64 (0.25)
1-Back	-0.40 (0.17)	-0.52 (0.25)	-0.64 (0.41)
2-Back	0.01 (0.25)	-0.12 (0.28)	-0.34 (0.27)
Item Recognition	0.62 (0.19)	0.54 (0.36)	0.78 (0.42)

Table 2.2 : Mean criterion across groups for the N-back and recognition memory tasks

2.4.2.2 Speed of Comprehension

There was a significant drug x time interaction [$F(2, 51) = 11.72$ $p<0.001$] and main effect of time [$F(1, 51) = 4.93$ $p<0.03$] on the number of completed sentences. Contrasts revealed that the placebo group completed more sentences than the 0.8 mg kg^{-1} and 0.4 mg kg^{-1} ketamine group [$t(51) = 4.03$ $p<0.001$] and significantly more sentences completed in the low dose ketamine compared to the high dose group [$t(51) = 2.68$ $p = 0.01$]. There was no effect of drug on number of errors in the speed of comprehension task or any interaction (See Fig 2.2).

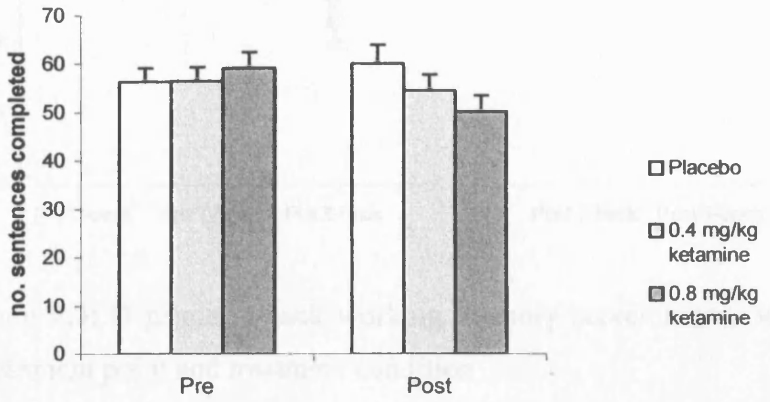


Figure 2.2: Mean number of sentences completed pre and post infusion across each treatment condition for speed of comprehension

2.4.2.3 N-Back Working Memory Task

For the N-back working memory data d' and C were also calculated. Analysis of d` with a 3 x 2 x 3 ANOVA yielded a significant time x drug interaction [$F(2, 51) = 7.49$ $p<0.01$] and a significant time x working memory load interaction [$F(2, 102) = 3.69$ $p<0.03$] in addition to main effects of working memory load [$F(1, 51) = 350.12$ $p<0.001$], time [$F(1, 52) = 10.18$ $p<0.01$] and drug [$F(2, 51) = 4.08$ $p<0.03$]. Further analysis of this data demonstrated group differences post-drug on the 1-back [$F(2,53) = 5.58$, $p<0.01$] and 2-back tasks [$F(2, 53) = 6.32$ $p<0.01$] only (See Fig 2.3).

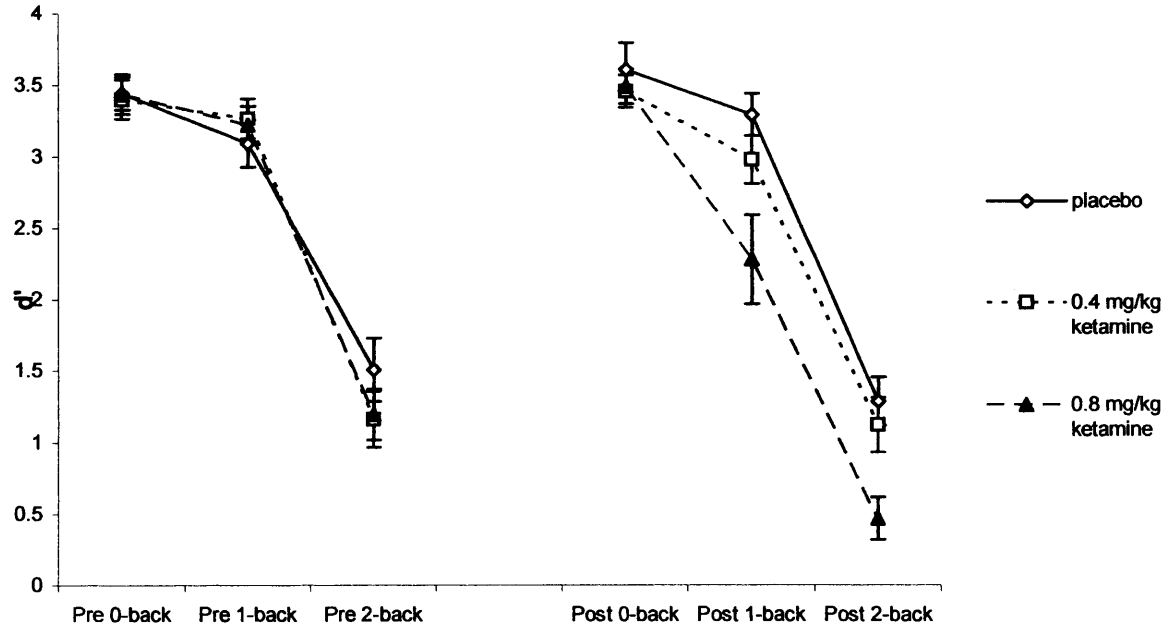


Figure 2.3: D prime N-back working memory scores across working memory load , assessment point and treatment condition

Contrasts indicated that these difference were attributable to lower scores in the drug groups compared to placebo on both the '1 back' [t(51) = 3.71 p=0.001] and '2 back' [t(53) = 2.34 p<0.03] tasks and lower scores in the 0.8 mg kg $^{-1}$ than the 0.4 mg kg $^{-1}$ ketamine group again both on the 1-back [t(53) =2.25 p<0.03] and 2 back [t(53) = 2.71 p<0.01]. As can be seen from Figure 2.3 the high dose ketamine group was performing at levels close to chance in the 2-back condition post-drug. The response criterion (C) also was analysed (See Table 2.2). A working memory load x drug interaction was found [F(4, 102) = 6.00 p<0.001], and a working memory load x time interaction [F(2, 102) =189.414 p<0.001] in addition to main effects of working memory load [F (2, 102) = 110.21 p<0.001] and time [F(1, 51)= 373.41 p<0.001]. Differences between groups were revealed post-drug on the 2-back section of the task[F(2,53)= 7.61

$p<0.01$]. The drug groups were less conservative overall than the placebo group [$t(53)=3.07$ $p<0.01$] and the high dose group was less conservative than the low dose group [$t(53)= 2.45$ $p<0.02$], (Group means, post drug were: placebo: 0.014 ± 0.25; 0.4 mg kg^{-1} ketamine: -0.12 ± 0.28; 0.8 mg kg^{-1} ketamine: $- 0.34 \pm 0.27$). Reaction times (RTs) were not found to differ between the groups at any of the time points. There was however a main effect of working memory load [$F(1, 51) = 147.24$ $p<0.001$]. Within subjects contrasts revealed RT's to increase with increasing memory load [$F(1, 43) = 199.73$ $p<0.001$] (See Appendix, Table A1 for mean RTs).

2.4.2.4 LOP Retrieval Intentionality (Table 2.3)

Word- stem completion: Participants completed more word stems with studied than unstudied words, i.e. priming occurred, with a main effect of study Condition [$F(1, 53) = 50.47$ $p<0.001$]. The ratio of targets to distractors completed was computed as an index of priming. RMANOVA of these scores for semantically encoded stems and physically encoded stems revealed no effects of drug or encoding condition on priming.

Cued Recall: Unlike the word stem completion condition encoding condition (semantic versus physical) had a significant effect on stem cued recall [$F(1, 51) = 19.53$ $p<0.001$] with semantically encoded words being better recalled than physically encoded words. There was a trend for a main effect of Drug [$F(2, 51) = 2.83$ $p =0.068$].

In the 'awareness' test at the end, n=4 subjects reported being aware of having seen the words before (placebo =2, low dose = 2).

2.4.2.5 Serial Reaction Time Task

The two sequences which participants were trained on were combined in the analysis. RTs are only used for trials on which participants did not make errors and RTs from the first two trials of each block were disregarded because it would be impossible for participants to predict the location of the next target. A 3x2x3 RMANOVA found a significant Block x Drug interaction [$F (4,106) = 3.55$ $p<0.01$ $p = 0.009$], significant main effects of probable/improbable [$F(1, 53) = 13.51$ $p<0.01$] and drug [$F (2,53) = 8.59$ $p<0.01$]. Post hoc Dunnett's t revealed the placebo group to be significantly faster than the 0.4 mg kg^{-1} ketamine group [$p<0.02$] and the 0.8 mg kg^{-1} group [$p<0.001$].

Paired comparisons (with applied Bonferroni correction) revealed significant differences between in reaction time between Blocks 1 and 2 in the placebo group[[$t(17) = 3.056$, $p<0.007$] and in the high dose group between Blocks 2 and 3 [$t(17) = 4.07$, $p<0.001$]. As can been seen from Figure 2.4, these reflect an decrease in reaction time in the placebo group from Block 1 to Block 2 and an increase in reaction time in the high dose ketamine group from Block 2 to Block 3.

Treatment	Targets Completed	Distractors Completed	Targets: Distractors	Target Recall
Placebo				
Overall	12.44 (2.77)	7.56 (2.47)	1.86: 1 (0.79)	8.56 (4.36)
Semantic	6.17 (2.24)			5.06 (2.48)
Physical	6.28 (1.82)			3.50 (2.44)
Low dose ketamine				
Overall	9.94 (2.36)	6.22 (2.21)	1.94: 1 (1.37)	7.61 (4.5)
Semantic	4.44 (2.73)			4.50 (2.38)
Physical	5.50 (2.46)			3.11 (2.78)
High dose ketamine				
Overall	10.27 (3.75)	7.56 (2.48)	1.63:1 (1.17)	5.33 (3.61)
Semantic	5.39 (2.83)			3.33 (2.30)
Physical	4.88 (2.11)			2.00 (1.94)

Table 2.3: Group means and standard deviations for(left to right): targets completed, distractors completed, ratio of targets completed to distractors completed, targets recalled

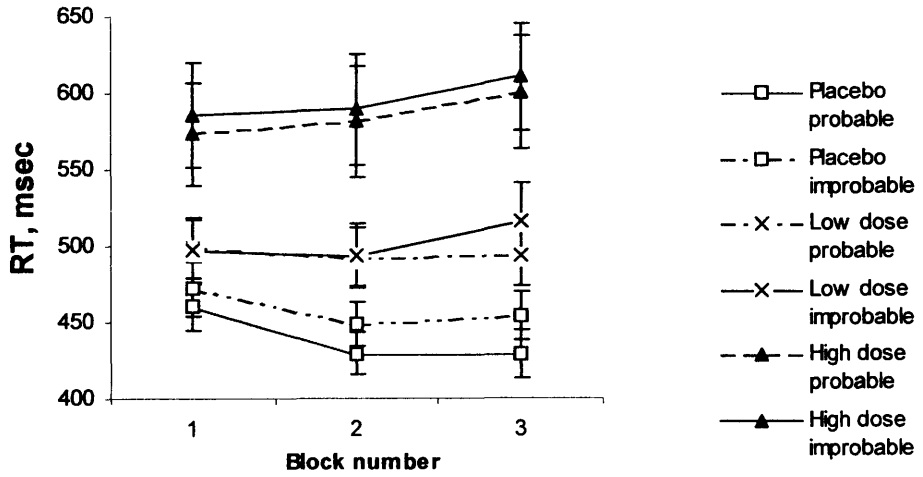


Figure 2.4: Mean RT's for the serial reaction time task across probable and improbable trials

Analysis of the mean number of errors per block yielded a significant effect of Condition [$F(1,53) = 6.12$ $p < 0.02$] and a significant main effect of Block [$F(2,106) = 4.38$ $p<0.02$]. However multiple comparisons did not demonstrate any further differences.

2.4.2.6 Trailmaking

For time taken to complete part A there were no significant group differences although there was a trend for a Time x Drug interaction [$F(2, 51) = 2.65$ $p=0.08$]. In part B there was a significant Time x Drug interaction for time taken to complete the task [$F(2, 51) = 5.73$ $p<0.01$]. Contrasts demonstrated were greater time taken to complete the task by the two drug groups compared to placebo [$t(51) = 2.50$ $p<0.02$] and in the 0.8 mg kg^{-1} ketamine group compared to the 0.4 mg kg^{-1} ketamine group post drug [$t(51) = 2.81$ $p<0.01$]. An overall score for trailmaking was computed by subtracting the scores from

the first part of the test from scores on the second part of test. This was to remove any general motor impairment effects from the task and concentrate upon the executive functioning component. Overall no significant effects of treatment condition, assessment point or errors were observed. (See Table 2.4)

	Placebo	Low dose	High dose
Pre drug			
Trails A, time taken sec	35.69 (17.25)	37.89(15.41)	34.65 (10.46)
Trails A, no. errors	0.11 (0.47)	0	0
Trails B, time taken sec	54.44 (18.76)	53.12(15.47)	51.53(21.20)
Trails B, no. errors	0.83 (2.71)	0.22 (0.94)	0.67(1.78)
Post drug			
Trails A, time taken sec	31.65 (10.99)	38.11 (12.90)	43.50(17.00)
Trails A, no. errors	0	0	0
Trails B, time taken sec	50.15 (15.46)	54.83 (17.83)	71.12(26.62)
Trails B, no. errors	0.67 (2.06)	0.72 (1.84)	4.11(6.98)

Table 2.4: Trailmaking data pre and post drug across treatment condition

2.4.3 Subjective Effects

2.4.3.1 Schizotypal Symptomatology (See Table 2.5) Data for schizotypyal symptoms were not normally distributed so were transformed by a square root transformation. However this did not affect the results of the RMANOVA's so untransformed statistics and means are reported. When the overall score for schizotypyal symptoms was computed, RMANOVA demonstrated a significant Drug x Time interaction [$F(2, 51) = 10.95$ $p<0.001$] and a significant effect of Time [$F(1, 51) = 23.26$ $p<0.001$]. Contrasts showed that both the drug groups scored more highly than the placebo group [$t(51)= -4.63$ $p<0.001$] but there were no differences between the 0.4 and 0.8 mg kg -1 ketamine groups.

2.4.3.2 Adapted Dissociative States Scale (See Table 2.5) RMANOVA of the overall ADSS score showed a significant Drug x Time interaction [$F(2, 51) = 21.30$ $p<0.001$] and significant main effects of Drug [$F(2, 51) = 17.28$ $p<0.001$] and Time [$F(1,51) = 85.63$ $p<0.001$]. Ketamine induced clear, dose-related dissociative effects. These were confirmed by further analysis of the interaction which revealed significantly lower scores in the placebo group compared to the two drug groups post-drug [$t(51) = -5.88$ $p<0.001$] and the 0.4 mg kg -1 ketamine group compared to the 0.8 mg kg -1 ketamine group post-drug [$t(51) = -2.85$ $p<0.01$ $p=0.003$].

	Placebo	Low dose	High dose
ADSS total score pre	1 (1.28)	1.06 (1.66)	3.17 (7.67)
ADSS total score post	2.33 (3.20)	15.28(11.23)	27.28(15.91)
SSQ total score pre	6.89 (10.63)	4.78 (6.79)	6.89(10.39)
SSQ total score post	4.61 (4.49)	14.39 (14.56)	18.61 (9.99)

Table 2.5 Means(standard deviations) of scores across treatments for the Adapted Dissociative States Scale (ADSS) and Schizotypal Symptomatology Questionnaire (SSQ) pre and post drug

2.4.3.3 Subjective Drowsiness: A 3x4 RMANOVA of the visual analogue scale for 'drowsiness' yielded a significant Drug x Time interaction [$F(6, 153) = 7.90$ $p<0.001$], a significant main effect of Drug [$F(2, 51) = 9.22$ $p<0.001$] and Time[$F(3, 153) = 67.93$ $p<0.001$]. Contrasts revealed that the placebo group were less drowsy than the two drug groups 10 min post drug [$t(51)=-5.30$ $p<0.001$], and 80 min post drug [$t(51) = -6.19$ $p<0.001$].

2.4.4. Correlations

As an attempt to investigate the link between schizophrenic-like symptoms and cognitive impairments correlations were conducted on key measures that demonstrated

impairments (source memory, speed of comprehension, N-back) in the high dose ketamine group. There were trends, after Bonferroni correction for a correlation between scores post drug on the SSQ and d' for recognition memory (r=0.493, p=0.038) and time to process sentences on the speed of comprehension task (r =0.479, p=0.045).

Guess on Treatment: The high dose ketamine group were all accurate in discriminating the drug from placebo, and 16 (89%) of the low dose participants could discriminate the ketamine from placebo. The experimenter guessed incorrectly as to the treatment condition (placebo/ low dose/ high dose) 20 times (high dose group 8/18 times, low dose group 8/18 times, placebo 4/18 times), thus the experimenter was accurate 63% of the time.

Gender Differences: No drug x gender interactions emerged on the source memory task, speed of comprehension and the schizotypal symptomatology questionnaire.

Plasma ketamine levels: At 65 minutes, mean plasma ketamine levels were 128.96 (±36.96) ng/ml for the low dose group and 261.90 (±31.56) ng/ml for the high dose group.

Other Responses: Seven participants reported feeling nauseous (high dose – 2 males, 4 females, low dose -1 male). Of these, one low-dose male participant vomited 5 minutes after the infusion had been stopped. However all participants, when asked, felt able to continue with the tasks. Many participants in the ketamine groups reported visual changes such as blurred vision or a sense that everything was moving or flickering. Despite this however all participants felt they were able to proceed with the tasks.

2.5 Discussion

The present study investigated the effects of two doses of ketamine, 0.4 mg kg^{-1} and 0.8 mg kg^{-1}, on memory systems, and dissociative and schizotypal symptoms. The

main findings were that ketamine impaired working and episodic memory with increasing dose, disrupted procedural and semantic memory regardless of dose whilst leaving perceptual priming intact. Ketamine also induced schizophrenic and dissociative symptoms, replicating previous studies (Krystal et al., 1994; Malhotra et al., 1996; Newcomer et al., 1999; Adler et al., 1999; Hetem et al., 2000).

Ketamine dose-dependently increased both source and recognition memory errors. These findings replicate the impairment in recognition memory observed previously with ketamine (Ghoneim et al., 1985; Malhotra et al., 1996; Hetem et al., 2000) but extend these findings to demonstrate an episodic memory impairment. The only previous study to examine episodic memory following ketamine indicated a decrease in both recollection and familiarity (Hetem et al., 2000; *subsequent to writing Honey et al., submitted*). There clearly is a parallel between impairments to conscious awareness ('remembering') and the source memory impairments we observed. Our finding of source memory deficits indicates not only an impairment of 'what' is remembered but also 'how, why and where'. This supports the notion that the NMDA-receptor is important in episodic memory in humans. Neuroimaging studies suggest that these deficits in source memory may be a function of hyperactivation of the prefrontal cortex and underactivation of the hippocampus and medial temporal lobe structures as these areas are associated with source memory (Wheeler et al., 1997) and this pattern of neural activity has been found following ketamine administration (Breier et al. 1997; Vollenweider et al., 1997).

Interestingly, the high dose ketamine group, whilst impaired, were still performing well above chance levels on the source memory task. Many previous studies have found recognition memory to be at chance following a similar dose of ketamine to that used in this study (e.g. Malhotra et al., 1996; Hetem et al., 2000). The elaborative encoding procedure used in this task, where source was associated with both gender of voice and subsequent semantic judgement, appeared to elevate source memory scores pre-drug to near-ceiling levels. This elaborative encoding, post-drug, may also have acted to partially compensate for ketamine-induced encoding impairments.

Working memory was dose dependently impaired in the present study, accompanied by a preservation of sustained attention. This finding replicates the work of Adler et al. (1998). Preserved attentional processes following ketamine administration eliminate the possibility that memory impairments are due to any general impairment in attentional functioning. It is also important to remember, when considering all the cognitive findings of the current study, that no one task taps a single memory system, for example impaired working memory observed here may also be partially responsible for the deficits on the episodic memory task.

Our findings provide the first demonstration that perceptual priming is preserved following ketamine administration. The levels of processing manipulation was successful and demonstrated a dissociation in performance on the implicit and explicit aspects of the task, satisfying Schacter's (1989) 'retrieval intentionality criterion'. Thus, on word-stem completion, levels of processing did not affect performance, but on cued recall they did, with semantically encoded words being better remembered than physically encoded words. There was a trend towards lower scores in the ketamine groups on the cued recall task in line with previous research demonstrating that cued recall is less sensitive to drug-induced impairment than free recall (Bishop & Curran, 1995). Interestingly, levels of cued recall were lower than stem completion throughout but lowest in the high dose ketamine group where twice as many stems were completed with targets in the implicit compared to explicit task. This would accord with the suggestion that in situations where conscious awareness is impaired, it may serve to have inhibitory effects on explicit memory (Danion et al., 1999). Preserved perceptual priming is of interest as no previous study has examined the effects of ketamine on this form of memory. This implies that a specific pattern of memory deficits is induced by ketamine rather than a global impairment on all memory tasks. Further investigation of priming with tasks such as process dissociation, that taps awareness in addition to priming, may be useful in interpreting these findings further.

It is interesting to note that even though both priming and procedural learning tap processes that do not involve conscious awareness, different findings were observed on these tasks. In patients with organic memory disorders, such as the amnesias, non-conscious forms of memory are generally preserved. The finding of impaired procedural learning in the presence of preserved priming observed in the current study, is reminiscent of the cognitive pattern observed in Parkinson's Disease (Jackson et al., 1995). However, evidence for a true impairment to procedural learning is unclear, as the reaction times of the ketamine subjects were significantly slower than those of placebo overall. Speed of responding may putatively affect learning, slower responses may mean that participants require longer to learn the sequence. Ketamine also reduced psychomotor speed on trailmaking in the present study but did not affect trailmaking scores once psychomotor slowing had been controlled for. This replicates the findings of Harborne et al. (1996) and indicates a preservation of some aspects of frontal functioning.

Retrieval from semantic memory was examined in the present study using the speed of comprehension task. There was a dose response relationship between the number of sentences verified on this task. This may suggest semantic memory impairments following ketamine administration. However participants did not make any more errors after ketamine. In light of the trailmaking results discussed above and those stemming from the SRT where reaction times and speed were significantly slower in the ketamine group, it is again possible that ketamine effects on this task are due to general psychomotor slowing attributable to the anaesthetic and sedative effects of the drug.

The current study replicated the findings of previous work in revealing an increase in the schizophrenic like and dissociative symptoms following ketamine. These findings confirmed that the psychotomimetic effects of ketamine are detectable on both clinician and self-rated scales, and that ketamine, in the doses administered in this study, induced a state resembling some of the symptoms of schizophrenia. There have been suggestions in the literature that, as NMDA-antagonists induce psychotic symptoms and the NMDA-receptor is involved in memory, the cognitive deficits observed in

schizophrenia may be mediated by the NMDA-receptor (e.g. Newomer & Krystal , 2001). Whilst cognitive impairment in schizophrenia still remains ill-defined, highly tentatively it appears that the profile of cognitive effects of ketamine appears somewhat similar to that observed in schizophrenia and organic psychosis (Perlstein et al., 2001) but differs in impairments to procedural learning and preserved executive functioning. Moreover there was some indication that schizophrenia like symptoms were related to semantic and recognition memory deficits, in contrast to previous work which has shown a relationship between working memory and schizophrenia-like symptoms (Adler et al., 1998). Further research using techniques such as pharmacological functional magnetic resonance imaging may shed light on the similarity between neuroanatomical substrates of NMDA-antagonist induced cognitive impairments and those observed in schizophrenia.

This study was subject to several limitations. Firstly, the cognitive testing began after 20 minutes, when ketamine may not have reached a plasma level comparable to that of previous ketamine research. This could explain the lack of errors on the speed of comprehension task, as this task was administered first. Secondly, the continuous infusion style used meant that ketamine levels may have been rising throughout the study, which could result in impairments on certain tasks being an effect of increasing dose rather than ketamine specificity for certain memory systems. Studies using steady state or pseudo-steady state infusion styles have negated this problem (Hetem et al., 2000; Newcomer et al., 1999). A consequence of rising blood ketamine levels may also have been that sedation was increasing which would have compounded the effects of ketamine on these tasks. However the data would seem to indicate that this is not the case. The tasks that were not affected by ketamine were towards the end of the battery, for example, implicit memory, when ketamine levels and drowsiness had increased. Furthermore, tasks at the beginning of the battery demonstrated ketamine-induced impairments (e.g. procedural learning). Thus it would appear that the selectivity of ketamine's effects on certain memory systems are not as a result of a test order that meant that tasks towards the end of the battery were subject to a combination of higher drowsiness and ketamine blood levels. Another limitation common to studies of this

kind, is that tasks may not be of comparable difficulty and whilst on tasks such as the N-back it is possible to manipulate levels of difficulty, on the other tasks this was not feasible. Despite this, these tasks have been shown to be differentially sensitive to the impact of pharmacological manipulations of memory systems.

The doses of ketamine used in this experiment are somewhat lower and involved a different infusion style (continuous rather than a bolus then maintenance infusion) than some used in previous studies (e.g. Krystal et al., 1994; Malhotra et al., 1996; Newcomer et al., 1999). Hence comparisons across these studies are limited. Despite this, however, the cognitive effects of ketamine observed in the current study were similar to those detailed in the aforementioned papers. As this study has demonstrated discernible ketamine effects at these doses, then future research may consider using lower doses, although by targeting a possibly lower steady state to further investigate memory systems and ketamine. There were no baseline differences between the groups which confirms that variation between the groups post-infusion is a result of drug effects and not individual differences. Previous studies have used crossover designs but as ketamine is associated with tachyphylaxis and potential residual cognitive effects were possible then the independent groups design was considered to be preferable.

In summary, the present study replicated previous data suggesting a ketamine-induced impairment of working memory and preservation of attention and executive function. This study extended findings of an impairment in episodic memory following ketamine by demonstrating an impairment in memory for source. Ketamine produced a slowing of semantic processing but no increases in errors. Further novel findings from this study were of preserved perceptual priming and impaired procedural learning induced by ketamine. This is a cognitive profile that differs from both schizophrenia and organic memory disorders.

Chapter 3: Source memory in ketamine users

Chronic effects of ketamine abuse: evidence for a persisting impairment of source memory in recreational users

"*The existence of forgetting has never been proved: We only know that some things don't come to mind when we want them.*"

Friedrich Nietzsche

3.1 Overview

Ketamine is an NMDA-receptor antagonist that is increasingly being used as a recreational drug. Previous work has shown gross generalised verbal memory impairments persisting 3 days after ketamine use in chronic users, however episodic memory has not specifically investigated in this population. The work presented in this chapter set out determine whether ketamine, on the night of drug use and 3 days later, is associated with impaired episodic memory as assessed by a source memory task. Twenty ketamine users and 20 poly-drug controls were compared on a source memory task both on day 0 and day 3. Participants also completed questionnaires on both days indexing schizophrenic-like and dissociative symptoms. On day 0, ketamine abusers were impaired on source memory and item recognition and scored more highly on schizophrenic and dissociative symptoms compared to poly-drug controls. On day 3 ketamine abusers only displayed source memory impairments and these positively correlated with the level of schizophrenic-like symptoms on day 0. No differences on day 3 in schizophrenic-like or dissociative symptoms were observed. Ketamine abusers exhibit a persisting deficit in source memory on day 3 but not item recognition. These findings suggest that repeated use of ketamine produces chronic impairments to episodic memory.

3.2 Introduction

A good deal of research has examined the acute effects of ketamine in healthy volunteers. However, relatively little is known about the effects of long-term ketamine abuse. In rats, repeated doses of NMDA-antagonists have produced persisting deficits in working memory performance (Jentsch et al., 1997b) and response inhibition (Jentsch et al., 1997a). A possible mechanism for these deficits is the neurotoxicity that has been found in rats administered of NMDA-receptor antagonists chronically. Repeated high doses of NMDA-antagonists induce neuronal degeneration in the posterior cingulate/retrosplenial cortex and other corticolimbic areas including the hippocampus, amgydala, and parietal, temporal, piriform and entorhinal cortices (Ellison & Switzer, 1993; Horvath & Buzsaki, 1993; Corso et al., 1997; Ellison, 1994). These neurotoxicity studies, however, used other non-competitive NMDA-receptor antagonists, such as phencyclidine (PCP) and dizocilipine (MK-801) with higher affinity for the NMDA-receptor than ketamine, The degree of neurotoxicity has been demonstrated to be related to the relative affinity to the NMDA-receptor (Olney et al., 1989) therefore neurotoxicity associated with repeated ketamine, whilst observable, is more subtle (Keilhoff et al., 2004a; 2004b).

There is some anecdotal evidence of persisting cognitive impairment in humans following ketamine abuse (Jansen, 1990; Lilly, 1978), however, only two studies have formally examined the cognitive effects of ketamine in recreational users of the drug. Curran & Morgan (Curran & Morgan, 2000) examined volunteers who reported taking ketamine with a population matched for poly-drug use, on the night of their ketamine use (day 0) and three days later (day 3). Day 0 effects replicated previous laboratory acute studies showing a broad range of cognitive impairments (e.g. Krystal et al. 1994) but three days later, participants were still impaired on tasks tapping episodic and semantic memory. A further study attempted to examine whether these day 3 effects were chronic or residual by comparing frequent and infrequent users of ketamine using a similar design (Curran & Monaghan, 2001). Episodic and semantic memory impairments were observed on day 3, as in the previous study, in the frequent but not

the infrequent ketamine users. These findings are suggestive of chronic effects of ketamine, as transient residual impairments would theoretically have been observed in both the groups.

The day 3 episodic memory impairments observed in those previous studies were tapped using a prose recall task. Although this task does examine memory for information learnt whilst on the drug, it cannot be regarded as a comprehensive episodic memory measure as performance on this task does not require explicit memory for the actual encoding context. Episodic memory can more appropriately be studied using source memory tasks. These require participants not only to recognise the information learnt i.e. 'what' was learnt, but also to recollect which source the information originally came from, in terms of everyday memory the 'how, where and when' component. For example, in daily life, impaired source memory is observed when one recognises a person's face but is unable to recollect where or when one previously met the person. In the laboratory, such tasks typically require the participant to remember which colour a word was presented in or whether it was spoken in a male or female voice. This aspect of episodic memory has been shown to be selectively impaired in certain disorders, for example, schizophrenia (Keefe et al., 1999; Vinogradov et al., 1997) and normal ageing (Schacter et al., 1994; Schacter et al., 1991; Wilding & Rugg, 1996). Previous research has demonstrated that an acute dose of ketamine in healthy volunteers impairs both item recognition and source memory (Morgan et al., 2004a) however three days later there was no impairment to either source or item memory (Morgan & Curran, unpublished observation). No research to date has examined source and item memory in chronic ketamine abusers.

Therefore this study was designed to investigate the acute and chronic effects of ketamine on episodic memory, using a source memory paradigm in ketamine abusers and matched polydrug controls on the night of drug use and three days later. We used the same source memory task in this study as we used in a study with healthy volunteers (Chapter 2; Morgan et al., 2004a). This allowed comparison between the acute effects of ketamine in healthy volunteers and chronic effects in abusers. Given

that chronic verbal memory impairments have already been demonstrated in ketamine abusers, we hypothesised that if these were due to a generalised memory deficit, then an impairment in both item recognition and source memory would be observed. However, if a selective deficit in the ability to encode, store or access contextual information about an event was responsible, then only a source memory impairment would be observed. Schizophrenic-like symptoms have also been found 3 days after drug use in ketamine users (Curran & Morgan 2000). Given the high incidence of source memory impairments in schizophrenia, we intended to investigate the relationship between these source memory failures and observed schizophrenic-like symptoms in ketamine-users.

3.3 Methods

3.3.1 Participants and design

Forty participants completed the study, 24 male and 16 female, recruited using a snowball sampling technique (Solowij et al., 1992) : 20 ketamine users (mean age: 23.1 ± 3.2 years, 9 females) and 20 polydrug using controls (mean age 23.9 ± 5.4 years, 7 females). Participants were tested on two occasions: on day 0, where the ketamine group were under the influence of the drug, and again 3 days later. Test versions were counterbalanced across group and day. The study was approved by the institutional ethical committee. Subjects were not paid for participation.

3.3.2 Procedure

Participants were approached in a party setting on day 0 and asked if they were interested in taking part in a study about drug users. If they agreed volunteers were taken individually to a quiet area where they informed the experimenter whether or not they had taken or intended to take ketamine that evening. They were then asked about other drug use and were excluded if they had taken any drugs other than small amounts of cannabis (< 1 "joint") or more than 2 units of alcohol that evening (n=5). Participants were also excluded if they currently only used cannabis or alcohol as it was necessary

to match the two groups for drug use (n=2). Participants on ketamine were asked to estimate when they had taken the drug, and only participants who had recently taken ketamine (i.e. within 10 minutes) were included. In addition, it was necessary to exclude 3 participants who had taken ketamine but then became unresponsive, due to large ketamine doses. Participants then completed the assessments detailed below and arrangements were made to meet up 3 days later. The task battery lasted a total of approximately 30 minutes. Participants were asked to abstain from using alcohol and other recreational drugs between the two test sessions. The follow-up test session on day 3 was carried out in the participant's home, in a room with minimal distraction. They then completed the same assessments as on day 0 along with a pre-morbid IQ measure and a detailed drug-use questionnaire. Participants had used similar amounts of alcohol and cannabis between day 0 and day 3 but 2 participants were excluded for ecstasy use between the two days. Participants provided written, informed consent on both days of testing, on day 0 after ketamine and again on day 3 when drug-free.

3.3.3 Assessments on day 0 and day 3

Source memory task (Wilding & Rugg, 1996): This task was chosen as an index of episodic memory. Stimuli consisted of 160 low frequency words. The words were divided randomly into 4 study lists of 40 words. Words were broadly matched across lists in terms of letters per word, imagery value and frequency. In each study list, half the words were spoken in a female voice and half in a male voice (allocation was randomly determined). Study words were presented to participants aurally, played on a tape recorder. During the study phase participants listened to each word, repeated it aloud and then, depending upon the gender of the voice it was presented in, rated the word as either pleasant/unpleasant or abstract/concrete. The gender of the voice and task associated with it was counterbalanced across conditions, as was the study list. After completing the list, there was a delay of six minutes, filled with another task, and then participants were presented with a test list of 80 words, 40 previously presented words and 40 words not seen at study. Test words were presented visually on a laptop screen. Participants were instructed to report whether the word presented was one that

they had heard before and if so, whether it had been presented in a male or female voice. Participants gave their responses verbally. Word recognition responses were recorded as hits, false alarms, misses and correct rejections. Source errors were also recorded.

Spot the word test (Baddeley et al., 1993): Participants were required to choose the real word out of pairs of words/non-words. This task has been shown to give a measure of IQ that is correlated 0.69 with the National Adult Reading Test (NART: (Crawford et al., 2001).

3.3.4 Subjective Ratings

Schizotypal Symptomatology Questionnaire (SSQ: Curran & Morgan 2000):
This is a 30-item questionnaire designed to assess state schizophrenic-like symptomatology, a purported disposition to schizophrenia or psychosis proneness. A higher score indicates a higher level of schizophrenic-like symptomatology.

Adapted Dissociative States Scale (ADDS): An adapted version of Bremmer et al.'s (1998) Clinician Administered Dissociative States Scale was used (Curran & Morgan 2000). This scale was a 19-point scale designed to assess dissociative states, with higher scores indicating higher levels of dissociation.

Visual Analogue Scales: A 16-item visual analogue scale was used to investigate mood symptoms (Bond & Lader, 1974). The scale yields three main factors: alertness, contentedness and calmness. A 15 item visual analogue scale was used to assess the subjective side effects of ketamine (See Appendix – A5). Items included were memory impairment, out of body experiences, visual distortion, sound distortion, altered time perception, dizziness, impaired concentration, depression, feelings of altered reality, impaired memory, nausea, bodily numbness, unsteadiness, lack of co-ordination and confusion. Ketamine subjects also rated their 'liking', 'feeling' and 'wanting' of the drug effects on day 0.

3.3.5 Statistical Analysis

Data from day 0 to day 3 were analysed using repeated-measures analysis of variance (RMANOVA) with day (0 or 3) as the within-subjects factor and group (ketamine or control) as between-subjects factors. Drug use patterns were compared using Mann-Whitney U-tests as these data were not normally distributed. χ^2 were used to analyse categorical data, such as educational level For the source memory task d prime {d' = [z(Ht') –z(Fa')]}, an index of discriminability, was calculated for the item recognition data, as was the criterion, C {C=[z(Ht') + z(Fa')]/ 2} an index of bias, using signal detection theory (Snodgrass & Corwin, 1988). Signal detection theory was used as it attempts to separate bias in responding, which is an important issue with drug users, from discriminability of stimuli. Correlations were performed between schizophrenic-like symptoms on day 0 and day 3 and source memory errors using Pearson's coefficient. Non-significant main effects and interactions are not reported.

3.4 Results

3.4.1 Demographics and Drug Use

The two groups did not differ significantly in age, education level (higher- control:12, ketamine :11; further - control:4, ketamine 7; School leavers at 16 - control:4, ketamine:2) or pre-morbid IQ as assessed by the 'Spot the Word' test (control - 51.75± 3.86; ketamine – 51.40± 4.50). Groups were matched on lifetime prevalence of drug use (Table 3.1) and differed only on years of use for LSD/hallucinogens [$F(1,38) = 3.64$ $p < 0.01$], mean days used per month for amphetamine [$U= 107$ $p < 0.01$] and mean days of use per month of LSD/hallucinogens [$U= 94.5$ $p < 0.01$]. All of the above differences were attributable to greater drug use in the ketamine group. Additionally, 2 controls and 2 volunteers from the ketamine group reported having taken benzodiazepines, 1 control reported using γ-hydroxybutyrate (GHB) and 2 participants from the ketamine group reported use of heroin but all had only tried these drugs once.

35% of the ketamine group participants reported that they had been using ketamine for 5 years, 30% for 4 years, 30% for 2 years and the remaining5 % for 3 years. The mean number of days per month the ketamine group used the drug was 13.05 (±9.05). The mean dose reported was 1.42g (±0.87). None of the control group reported ever taking ketamine.

	Years of drug use		Dose used per session/day*		Number of days used per month (30 days)	
	Control	Ketamine	Control	Ketamine	Control	Ketamine
Alcohol	7.45 (5.09)	7.40 (2.52)	7.05 (3.87)	7.15 (3.59)	19.10 (8.38)	22.80 (6.37)
Cannabis	5.40 (4.66)	5.60 (3.28)	2.80 (1.91)	5.65 (5.02)	23.20 (11.59)	21.35 (11.45)
MDMA	3.55 (2.04)	4.25 (1.74)	2.80 (1.74)	3.40 (1.60)	2.85 (1.60)	3.60 (1.88)
Amphetamine	2.80 (3.21)	3.05 (2.67)	0.64 (0.96)	0.57 (0.41)	1.05 (1.54)	2.75 (2.31)
LSD/ Hallucinogens	1.20 (1.91)	2.93 (2.74)	0.80 (1.01)	1.48 (1.35)	0.60 (1.05)	2.40 (2.54)
Cocaine	2.75 (2.67)	2.15 (2.18)	1.01 (0.97)	0.63 (0.65)	2.35 (2.7)	2.55 (2.72)

*MDMA and LSD were reported per tablet, alcohol per unit, tobacco and cannabis per cigarette smoked and cocaine, amphetamines and ketamine per gram.

Table 3.1: Mean (s.d) for drug use in the ketamine and control group : dose, years of use and 30 day prevalence.

On day 0 all of the ketamine group and none of the control group reported ketamine use. Both groups had also used alcohol (<2 units) and cannabis (<0.28g/ 1 'joint') on

day 0. There were no group differences in alcohol or cannabis use on day 0. Participants did not report any drug use between day 0 and day 3.

3.4.2 Cognitive Tasks

3.4.2.1 Source Memory

A RMANOVA of d′ data (discriminability) yielded a highly significant day x group interaction [$F_{(1,38)} = 9.38$ $p < 0.004$] and a main effect of group [$F_{(1,38)} = 8.40$ $p < 0.006$]. Post-hoc simple effects analyses showed that the ketamine group had significantly lower means than the control group on day 0 [$t_{(38)} = 3.55$ $p < 0.01$], but there was no significant difference between the ketamine and control group on day 3 (Figure 3.1a).

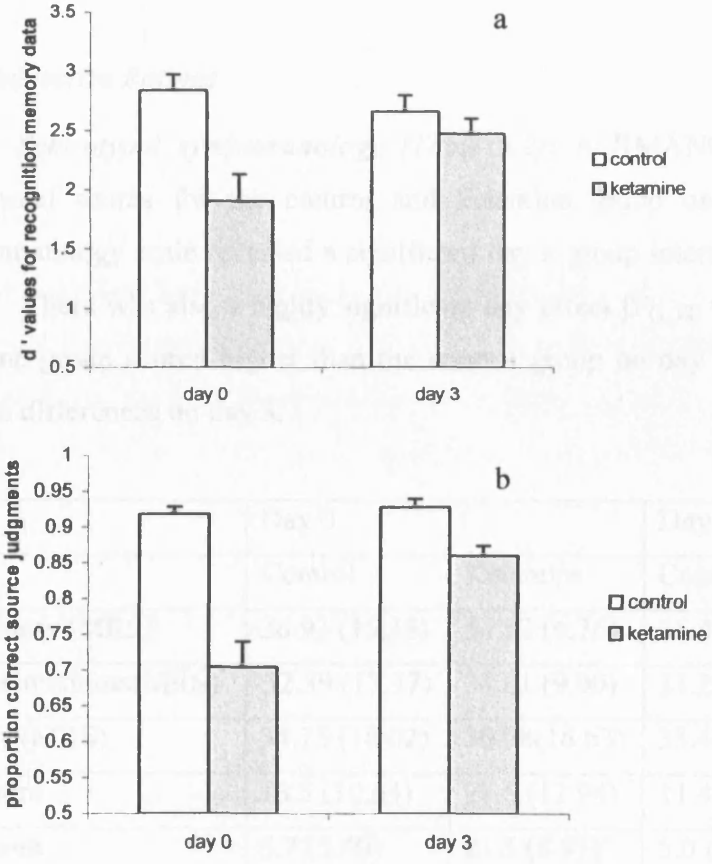


Figure 3.1a: d′ values for recognition memory data across day 0 and 3 for ketamine users and poly-drug controls; Figure 3.1b: Proportion of correct source judgments across day o and day 3 for ketamine users and poly-drug controls

An RMANOVA conducted on the criterion, C, data (response bias) showed a trend towards an interaction between day and group [$F_{(1,38)}$ = 3.24 p < 0.08], but no main effects of day or group. In terms of source memory, as seen in Figure 3.1b, the ketamine group were performing above chance (0.5) on both days. However, even though they improved on day 3, they were still significantly impaired compared to controls. RMANOVA of the proportion of correct source judgements given correct item recognition (Ht/Ht') revealed a significant day x group interaction [$F_{(1,38)}$ = 13.15 p< 0.001] and a significant main effect of day [$F_{(1,38)}$ = 18.05 p< 0.001]. Post-hoc analyses found that the ketamine group produced more source errors both on day 0 [$t_{(38)}$ = 5.96 p < 0.001) and on day 3[$t_{(38)}$ = 3.84 p < 0.001] (Figure 3.1b).

3.4.3 Subjective Ratings

3.4.3.1 Schizotypal symptomatology (Table 3.2): A RMANOVA conducted on the mean total scores for the control and ketamine group on the schizophrenic-like symptomatology scale revealed a significant day x group interaction [$F_{(1,38)}$ = 39.80 p< 0.001]. There was also a highly significant day effect [$F_{(1,38)}$ = 42.63 p< 0.001]. The ketamine group scored higher than the control group on day 0 as expected but there were no differences on day 3.

	Day 0		Day 3	
	Control	Ketamine	Control	Ketamine
Drowsiness (MRS)	36.93 (15.18)	54.53 (6.76)	35.42 (14.65)	35.31 (15.42)
Discontentedness(MRS)	32.39 (17.37)	34.61 (9.90)	31.25 (17.65)	28.14 (11.58)
Anxiety (MRS)	34.75 (18.02)	30.98(16.63)	35.48 (20.08)	27.88 (14.59)
SSQ score	13.5 (10.64)	27.6 (12.94)	11.4 (8.40)	9.2 (7.46)
DSS score	5.7 (5.40)	21.5 (8.91)	5.0 (5.56)	1.6 (3.02)

Table 3.2: Mean (s.d) scores for subjective effects scales in ketamine (n=20) and control (n=20) groups on day 0 and day 3 of testing

3.4.3.2 Adapted Dissociative States Scale (Table 3.2): Total ADSS score also showed a significant group x day interaction [$F_{(1,38)}$ = 41.36 p< 0.001] and main effect of day [$F_{(1,38)}$ = 45.54 p< 0.001]. The ketamine group had similar scores to the control group on day 3, but much higher scores on day 0.

3.4.3.3 Visual Analogue scales

MRS: The Mood Rating Scale yields three factors, drowsiness, discontentedness and anxiety. RMANOVAs were carried out on each of the mood factors. The factor of drowsiness showed a significant group x day interaction ($F_{1,38}$=9.12, p=0.004) and main effects of both day ($F_{1,38}$=12.49, p=0.001) and group ($F_{1,38}$=7.96, p=0.008). Table 3.2 shows the mean sedation levels rated by each group on both days. A post hoc analysis revealed that ketamine users rated higher levels of sedation on day 0 (p<0.001), but there was no group difference on day 3. There were no differences between the groups on the other mood factors.

Subjective Effects Scale: The data from the Subjective Effects Scale are summarised in Table 3.3. Significant differences were found on each of the factors on day 0, except for depression and nausea. The ketamine group rated higher symptoms on the other 12 scales on day 0. There were no group differences on day 3. (See also appendix 1 for p values). On day 0, ketamine users rated themselves as liking the drug [mean = 80.5 ± 16.65]; wanting more of the drug [mean = 62.34 ± 24.32] and feeling the effects of the drug [mean = 50.6 ± 34.32]. Liking [mean = 65.76 ± 28.24] and wanting the drug [79.34 ± 29.21] on day 3 did not differ significantly.

3.4.4 Correlations

Schizotypy scores on day 0 were significantly correlated with source memory errors on day 0 (r=0.702, p=0.001) and day 3 (r=0.535 p=0.015) but no correlation was found between schizotypy scores on day 3 and source memory errors.

	DAY 0		DAY 3	
	Control	Ketamine	Control	Ketamine
Dizziness	6.70 (7.48)	41.00 (25.25)	6.45 (7.28)	6.35 (11.66)
Altered time perception	8.10 (7.48)	37.40 (25.91)	7.95 (9.46)	7.85 (15.62)
Impaired concentration	18.80 (15.04)	52.45 (21.09)	14.75 (14.36)	10.35 (14.28)
Altered reality	10.55 (13.32)	43.70 (31.60)	8.25 (11.17)	9.15 (15.10)
Depression	10.70 (12.02)	19.45 (17.90)	7.75 (7.72)	11.00 (14.64)
Impaired memory	11.25 (16.60)	37.55 (22.92)	8.70 (11.90)	9.50 (15.66)
Nausea	7.65 (8.44)	19.65 (22.97)	8.85 (9.18)	7.35 (11.63)
Visual distortion	8.80 (10.50)	41.75 (26.96)	8.55 (9.32)	8.90 (17.08)
Bodily numbness	4.55 (4.94)	43.30 (28.02)	3.80 (3.94)	8.30 (14.80)
Unsteadiness	8.35 (10.59)	50.85 (22.93)	6.15 (6.88)	9.25 (16.58)
Lack of coordination	10.15 (13.60)	48.55 (29.56)	9.35 (11.31)	8.65 (15.92)
Confusion	9.30 (9.82)	45.10 (26.51)	12.25 (18.72)	8.70 (20.44)
Distortion of sound	2.70 (4.17)	36.80 (23.53)	2.00 (3.32)	10.95 (21.53)
Out-of-body experience	2.55 (3.71)	25.60 (29.09)	3.70 (7.08)	7.85 (13.96)

Table 3.3: Means (s.d.) scores on the bodily symptoms ratings by the ketamine and control groups.

3.5 Discussion

The two major findings of this study were that, on the night of drug use, both source and recognition memory were impaired in ketamine abusers, but 3 days after an acute dose of ketamine source memory was selectively impaired alongside intact item recognition. This extends previous findings of day 3 impairments to prose recall in ketamine abusers but indicates that this finding is not a generalised memory deficit but rather a specific detriment in recollecting contextual information associated with, and necessary for, episodic memory. By using exactly the same source memory task as has been used in the laboratory with healthy volunteers (Chapter 2), this allows for some degree of, albeit purely descriptive, comparison across the two populations. The chronic ketamine users exhibited a similar degree of impairment as observed in healthy volunteers given 0.8 mg/kg ketamine (over 80 mins) on day 0, but on day 3 the source memory impairment in ketamine abusers resembled that seen in healthy volunteers on day 0 following 0.4 mg/kg ketamine. The doses used by ketamine abusers in this study were considerably higher than the dose given in the laboratory (0.8 mg/kg ketamine) and yet memory impairments were similar on day 0. This may indicate some degree of tolerance to the effects of ketamine builds up over repeated drug use.

There are 3 possible explanations for these persisting source memory impairments in ketamine abusers: residual effects, chronic effects and pre-existing differences in abusers compared to controls. Residual acute ketamine effects seem unlikely both because ketamine has a very short half-life (10-12 mins) with a terminal half life of 2-3 hours and because our laboratory study with healthy volunteers on the same source memory task found no day 3 residual impairments to source or recognition memory (Morgan & Curran, unpublished observation). Thus chronic effects of repeated ketamine may be a more plausible interpretation, given previous findings of day 3 impairments in frequent, but not infrequent, users of ketamine (Curran & Monaghan 2001). The participants in the current study were using similar approximate doses to the frequent users described by the latter authors. At the same time, whilst our

interpretation of the findings leans towards chronic effects of ketamine, it is impossible to rule out the potential of pre-existing differences in ketamine abusers and non-abusers without the use of prospective studies. However, the two drug using groups were matched on pre-morbid IQ, educational level, use of other memory impairing drugs (i.e. alcohol and cannabis) and both groups had similar schizophrenic-like scores and item recognition memory on day three. Thus the finding in the ketamine group of a day 3 source memory impairment seems likely to be attributable to chronic ketamine use.

Source memory impairments as observed in this study may potentially reflect neurotoxicity, as was found in rats following repeated doses of ketamine (Olney et al., 1989). However, neurotoxicity in rats was detected in diverse regions including the medial temporal and diencephalic structures, the integrity of which is thought to be important for successful recognition memory (Squire, 1994) The apparently selective nature of the source memory impairment on day 3 is interesting in light of the widespread distribution of NMDA-receptors in the brain and their putative role in memory.

Source memory has been demonstrated in neuroimaging studies to engage prefrontal regions (Buckner & Koustall, 1998; Fletcher et al., 1997; Rugg et al., 1999) and to be disproportionately poor in patients with damage to prefrontal regions (Shimamura & Squire, 1987; Janowsky et al., 1989). Thus the selective source memory impairment observed in this study may relate to findings in non-human primates and rats of persisting deficits on tasks that seem to rely on frontal functions following repeated NMDA-receptor antagonists (Jentsch et al., 1997b; Jentsch & Roth, 1999). It is possible that a similar impairment to frontal functioning occurs in human long-term ketamine abusers, especially in light of previous work demonstrating persistently impaired fluency in this population, another task thought to have a considerable frontal component (Curran & Morgan 2000; Curran & Monaghan 2001). The selective source memory impairment observed here invokes comparisons with other populations, in particular schizophrenia, where selective source memory impairments are also observed (Keefe et al., 1999). Indeed there have been suggestions in the literature that repeated

NMDA-receptor antagonist administration may provide a better model of schizophrenia than single dose (Jentsch & Roth 1999). The source memory impairment observed fits with this proposal but not the lack of day 3 schizophrenic-like symptomatology. However the possibility exists that chronic ketamine use represents a model of the chronic stages of schizophrenia where negative and cognitive symptoms dominate.

Acutely, schizophrenic-like and dissociative symptoms resembled those observed in the laboratory. No day 3 effects on these scales were observed. The finding of no day 3 diffferences schizophrenic-like symptoms concurs with some (Curran & Monaghan 2001) but not all (Curran & Morgan 2000) previous work with abusers. Possible explanations for the discrepancies in the findings of these three studies may be that the participants were using higher doses of ketamine and for a longer period than those in the Curran & Morgan (2000) study but a similar dose to that used by frequent ketamine abusers in the Curran & Monaghan (2001) study where no schizophrenic-like symptomatology was observed. Thus it may be that these heavier ketamine abusers have developed psychological tolerance to the psychotomimetic after-effects of the drug. In addition individual differences in response to ketamine, which appear to be considerable even in healthy humans (Krystal et al. 1994), may account for these discrepancies and may possibly linked to genetic differences (Malhotra et al. 1996).

Interestingly, the source memory impairments observed on day 3 and especially on day 0 were positively correlated with schizophrenic-like symptomatology on day 0 but not on day 3. This would seem to indicate that the degree to which the users experience the psychotomimetic effects of ketamine on day 0 is related to the degree to which they suffer persisting cognitive impairment. Subjective ratings of mood were not correlated with source memory, thus these cognitive impairments appear to be specifically related to the ability of ketamine to induce schizophrenic-like effects. These correlations may suggest that similar underlying processes are mediating the source memory impairments and schizophrenic-like symptoms observed in the current study in ketamine users. This could add weight to the chronic ketamine model of schizophrenia.

This study was also subject to several limitations, common to virtually all studies of recreational drug users (Curran, 2000). Whilst both groups were well matched on demographics and attempts were made to match groups on all aspects of drug use there were still differences in monthly consumption of amphetamines and LSD. This highlights an issue common to all recreational drug research, that inevitably in a population of poly-drug users it is difficult to attribute effects to one particular drug, and it is possible that drugs are interacting to produce complex effects. Furthermore, due to the naturalistic testing environment, it was not feasible to obtain urine or blood samples to verify self-reports of drug use. Despite these issues, however, the main difference between the groups in terms of drug use was ketamine use. None of the control group reported ever using ketamine, whilst the ketamine group reported using the drug frequently and on average once every two days. In addition, neither chronic use of amphetamine nor LSD has been reported to affect source memory. In fact, chronic amphetamine use has been shown to impair recognition memory (Ornstein et al., 2000), which was found to be preserved here. Moreover, the difference in days of use per month of these drugs between the groups was approximately one day. Further, the profile of subjective effects observed on day 0 in the present study (e.g. perceptual distortions, out of body experiences, bodily numbness) is largely unique to NMDA-antagonists and is in close accord with that observed in the laboratory, suggesting that the drug ingested by these drug users was indeed ketamine.

In summary, on day 0 under the influence of ketamine, chronic users displayed source and recognition memory impairments and schizophrenic-like, dissociative and subjective effects that resembled findings in the laboratory with healthy volunteers. However on day 3 the ketamine abusers exhibited no recognition memory impairment or schizophrenic-like or dissociative effects but did exhibit a selective impairment to memory for source. This may relate to preclinical work indicating that tasks tapping frontal function may be selectively impaired following chronic NMDA-receptor antagonists. Further work is required to examine the neuroanatomical substrates of these impairments and the effects of chronic ketamine on other frontal tasks such as

response inhibition. These findings have worrying implications for the growing population of ketamine abusers.

Chapter 4 : Semantic priming and ketamine

Semantic priming after ketamine acutely in healthy volunteers and following chronic self-administration in substance users

"The limits of my language are the limits of my mind. All I know is what I have words for"

Ludwig Wittgenstein

4.1 Overview

Ketamine is used acutely as a model of schizophrenia. It has been suggested chronic ketamine may also mimic aspects of this disorder, in particular impaired cognitive function. As semantic processing deficits are considered central to cognitive impairments in schizophrenia, this study aimed to characterize semantic impairments following both acute and chronic ketamine. We examined the acute effects of two doses of ketamine (Experiment 1) using a double-blind, placebo-controlled, independent groups design with 48 volunteers. Ketamine's chronic effects (Experiment 2) were explored in 16 ketamine users and 16 poly-drug controls. A semantic priming task with a frequency (high and low) and stimulus onset asynchrony (SOA: short–200ms, long–750ms) manipulation was used. In Experiment 1, acute ketamine produced inverse priming at the long SOA. In Experiment 2, ketamine users showed inverse priming for low-frequency words at the long SOA compared to poly-drug controls. The inverse priming effect at the long SOA induced by acute ketamine was indicative of controlled processing impairments. In ketamine users, there was also a suggestion of controlled processing impairments. Decreased priming for low-frequency words suggested that long-term ketamine abuse results in damage to the semantic store.

4.2 Introduction

In the cognitive domain, it has been widely demonstrated that a single dose of ketamine administered to healthy volunteers impairs working and episodic memory (Chapter 2; Krystal et al., 1994). However, its effects on the semantic memory system remain unclear. Most studies have tested the effects of ketamine on semantic memory using the category fluency task where impairments have been found in some (Abel et al., 2003a; Adler et al., 1998) but not all (Ghoneim et al., 1985; Chapter 6) studies.

Nearly all research on the cognitive consequences of ketamine concerns the effects of a single dose. This is despite the suggestion that chronic ketamine may provide a better model of facets of schizophrenia (Jentsch & Roth, 1999; Phillips & Silverstein, 2003). Although, repeated doses of this anaesthetic cannot be given to healthy volunteers, for ethical reasons, a naturalistic population is available for studying the chronic effects of this drug. As ketamine is increasingly a substance of abuse among young people, users who repeatedly self-administer the drug can provide a window on the effects of its repeated use.

Two studies have assessed the effect of repeated ketamine use on category fluency. At the time of ketamine use, users were impaired in category fluency compared to controls (Curran & Morgan, 2000). These impairments were distinct from those observed in acute ketamine studies in that they not only reflected a reduction in the number of words generated but also represented increased errors (e.g. given the category fruit, one user produced 'lemons, melons, Helen's....). Whilst less pronounced, impaired fluency was still evident when the users were drug-free, 3 days after their ketamine use. A subsequent study also showed a similar pattern of impairment, with greater deficits in more frequent ketamine users (Curran & Monaghan, 2001).

Whilst the category fluency task used in the above ketamine studies does tap the semantic memory system, it also requires sustained attention, working memory and overt retrieval strategies, processes that are impaired by ketamine (e.g. Morgan et al.,

2004a). Semantic memory deficits are considered to be central to cognitive impairment in schizophrenia by many researchers (Rossell et al., 2000). It is therefore important to determine the effects of ketamine on semantic memory using a task which loads on this system. Thus the focus of the present research is on semantic priming.

Semantic priming refers to the facilitation of responding to a word (e.g. table), when it is preceded by a semantically *related* word (e.g. chair) as compared with an *unrelated* word (e.g. sheep) (Neely, 1977; Meyer & Schvaneveldt, 1971; Fischler, 1977). Although semantic priming is more specific to the semantic memory system than other tasks, it still involves interactive processes. Initially, presentation of the word stimulus is thought to activate a node within the semantic memory network, subsequently activation from this node spreads to associated nodes, which facilitates processing of these words if they appear as targets. This process is thought to be automatic (Neely, 2004), i.e. occurring without conscious awareness. Other mechanisms hypothesised to be involved later in the processing of a word include expectancy effects and semantic matching (Neely & Keefe, 1989). Expectancy is the pre-lexical mechanism whereby a set of potential targets is generated from the prime. It is thought that the processing of words outside the expectancy-generated set is inhibited, leading to increased reaction times (RTs) for unrelated words. Semantic matching refers to the matching post-lexically of the primes and targets for semantic similarity. The presence or absence of a semantic relationship provides information about the lexical status of a word (Chwilla et al., 1998). Both expectancy and semantic matching are thought to be controlled processes, requiring conscious effort. Fortunately, it is possible to manipulate semantic priming paradigms to investigate these two types of processing. As automatic processing occurs early in the processing of a stimulus, using a very short time between the presentation of a prime and a target (stimulus onset asynchrony: SOA < 250ms), allows investigation of automatic processes. Likewise, at longer SOA's (<700ms) the action of more controlled processes can be explored.

Other parameters may also be manipulated in semantic priming tasks to yield valuable insights into the nature of semantic memory impairments. In semantic dementia,

patients who exhibit a progressive degradation of the semantic memory store 'lose' low-frequency words first (Warrington, 1975; Warrington & Cipolotti, 1996). However, certain aphasic patients have impaired access to semantic memory, and find low and high frequency words equally difficult to name (Warrington & Shallice, 1979). Thus, using high and low frequency words in a semantic priming paradigm could theoretically differentiate between impairments in access to, or storage of, semantic knowledge (Rossell et al., 2001). No previous research has examined semantic priming following either acute or chronic ketamine.

Therefore the aim of the current study was to examine semantic priming following acute ketamine administration in healthy volunteers (Experiment 1) and following repeated self-administration in recreational ketamine users (Experiment 2). Both short (250msec) and long SOA's (750msec) were used to partially differentiate automatic and controlled processes in semantic memory. Previous work has indicated a relative preservation of automatic processing following a single dose of ketamine (Chapter 2) and in recreational ketamine users (Curran & Morgan, 2000). We were unsure of whether this would generalise to semantic processing but speculatively hypothesized disrupted priming at the long SOA only, indicative of controlled processing deficits, for both Experiments 1 and 2.

This study also used low and high frequency stimuli to differentiate access from storage impairments. For Experiment 1 we predicted that any semantic memory impairments observed in healthy volunteers following an acute dose of ketamine would be due to problems accessing information rather than storage loss, thus they should show equivalent priming for both high and low frequency words. Previous research has suggested that chronic ketamine use may eventually degrade the semantic store (Morgan et al., 2004c) thus in Experiment 2 we tentatively predicted a selective impairment of priming for low-frequency words but not high-frequency words.

Experiment 1 – Acute effects of ketamine on semantic priming in healthy volunteers

4.3 Methods and Materials

4.3.1 Design

An independent groups design was used in which male and female participants were randomly allocated to receive an infusion with one of two doses of ketamine or placebo. The three groups were balanced for gender with 8 females and 8 males in each. Double-blind procedures were used throughout.

4.3.2 Participants

Participants were recruited through an advertisement and were paid for their participation. The study was carried out in accordance with the Declaration of Helsinki and was approved by the UCL/UCLH ethics committee. All participants gave written, witnessed, informed consent on two occasions: at screening and then at the beginning of the testing session. Screening of participants followed the same procedures as used in a previous study (Morgan et al., 2004a). Participants underwent a semi-structured interview to investigate psychiatric history and drug use was verified by urinalysis. Inclusion criteria were that participants were between 18 and 35 years old and native English speakers. Exclusion criteria were current, past or a family history of psychiatric disorders; substance misuse; and general health problems. 48 participants completed the study [mean age placebo: 24.33±4.30; low-dose 23.75±3.79; high-dose 24.31±4.54], 1 participant dropped out of the study during infusion of high-dose ketamine.

4.3.3 Drug Administration

A 16-gauge intravenous cannula was inserted in the non-dominant forearm. Ketamine infusion was via a Graseby intravenous infusion pump controlled by the Stanpump program (Schafer et al. 1990). The program uses a "BET" (bolus-elimination-transfer) infusion scheme that aims to achieve the target plasma concentration almost instantaneously by taking into account ketamine pharmacokinetics using a three

compartment model (Domino et al., 1984). Participants received either ketamine (low-dose or high-dose) or placebo (0.9% NaCl solution). A peripheral venous blood sample was taken 50 minutes after commencing the infusion. The blood sample demonstrated that target concentrations (originally 100ng/ml, 200ng/ml) were exceeded (mean plasma concentrations: low-dose: 113.4±56.7ng/ml and high-dose: 236.7±65.3ng/ml).

4.3.4 Procedure

Testing began at either 9am or 1 pm and the time of testing was matched across groups. Participants arrived at the hospital after completing an overnight fast for morning testing, or a minimum of six hours fasting for afternoon testing. They were assessed on the pre-drug battery for 20 minutes, then allowed to rest for 15 minutes and then were cannulated. Approximately 5 minutes after cannulation, the anaesthetist began the infusion. Participants were tested on the main battery of tests, including semantic priming, beginning 15 minutes after the start of infusion. Throughout the 60-minute infusion each participant's pulse, blood pressure and electrocardiagram were monitored. After infusion participants were provided with light refreshments and were assessed 30 minutes later and then at hourly intervals by the medical staff as to their 'street readiness' and were discharged approximately 2 hours following infusion. Participants were given the telephone number of a clinical psychologist and an anaesthetist in case of adverse after effects; none were reported.

4.3.5 Assessments

Semantic Priming

The stimuli were 360 concrete nouns and 120 pseudo-words. These were arranged in three conditions: related (e.g. bed-wardrobe: 60 word pairs), unrelated (e.g. bed–parsnip: 60 word pairs) and pseudo (e.g. bed-fips: 120 word pairs). Participants were presented with a prime word for 200ms, then, following an interval, were presented with the target word for 200ms (Figure 1). Participants could respond for 2000ms after the target was presented and between each trial (i.e. prime-target word pair) there was a blank screen for 2500ms. Half of the concrete nouns used were of a low frequency (1-

30 words per million) and half were high frequency (>30 words per million). These were arranged in prime-target pairs of the same frequency. The task was run with two different SOAs (time between the onset of a prime and a target): short SOA (250ms) and long SOA (750ms). The order of the trials were randomised, with the constraint that any given trial type could not occur more than three times consecutively. All stimuli were presented in the centre of a computer screen using DMDX (http://www.u.arizona.edu/~jforster/dmdx/official.htm) software. Subjects were asked to indicate whether the target was real or a pseudo-word a two-button press. Subjects were told to respond as quickly and as accurately as they could. RTs and accuracy were recorded automatically. Two matched versions were used, which were counterbalanced across gender and drug treatment group.

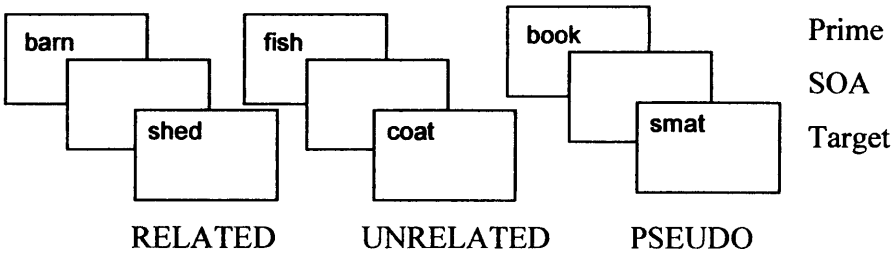


Figure 4.1 Schematic of design of semantic priming task

Subjective Effects

Participants completed the subjective effects questionnaires both pre drug (-10mins) and post drug (+ 40mins).

Adapted Dissociative States Scale (ADSS): This questionnaire was the subjectively rated items of the Clinician Administered Dissociative States Scale (Bremner et al. 1998) and assessed dissociation.

Schizotypal Symptomatology Questionnaire (SSQ: Curran & Morgan, 2000):

The 26-item self-rated questionnaire was employed to assess state schizotypal symptomatology.

4.3.6 Statistical Analyses

Semantic priming was initially analysed with a 3x2x2x2 RMANOVA with one between-subjects factor: Drug (high-dose ketamine, low-dose ketamine and placebo) and three within subjects factors: Frequency (high and low), Relatedness (related, unrelated), and SOA (short and long) using either mean RTs or mean % error data. When significant interactions emerged the level of priming effect was computed (unrelated - related) and used in subsequent analysis. Subjects making more than 20% errors were excluded however none met these criteria so all were included. In addition, RTs more than 2.5 s.d's from the overall mean for each subject were excluded, and RTs faster than 250msecs and slower than 1500msecs were discarded. *A priori* planned linear contrasts were conducted, to test for linear trends across placebo, low-dose and high-dose. Post-hoc Scheffé's tests were conducted on the subjective effects data, the significance level was Bonferroni corrected to account for multiple comparisons (α = 0.0167). Non-significant main effects and interactions are not reported.

4.4 Results

4.4.1 Trait Scores, Demographics and Drug dosage

There were no significant group differences in age, premorbid I.Q. (spot the word), trait depression, trait anxiety, alcohol use, tobacco use, or trait dissociation (See Table 4.1).

	Placebo	100 ng/ml ketamine	200ng/ml ketamine
Age, years	24.33 (4.30)	23.75 (3.79)	24.31 (4.54)
Years in education	17.93 (1.91)	17.06 (2.14)	17.80 (2.11)
Spot the word, no. words	51.46 (4.74)	51.83 (4.00)	50.53 (4.05)
BDI score	3.77 (5.39)	3.20 (3.80)	4.36 (5.35)
STAI score	13.46 (11.89)	17.30 (8.90)	17.50 (8.99)
DES score	23.00 (18.25)	20.30 (15.96)	23.90 (15.26)
Smokers, no. per group	5	8	7
Alcohol, units per week	12.20 (8.21)	14.44 (8.88)	16.07 (14.06)

[Abbreviations - BDI : Beck Depression Inventory; STAI : Speilberger Trait Anxiety Inventory; DES: Dissociative Experiences Scale]

Table 4.1: Demographic and background variables across treatment condition in Experiment 1

4.4.2 Semantic Priming Data

Reaction Time Data

Mean RTs for the 3 groups in each condition are shown in Table 2. There were two 3-way interactions: a Drug x Frequency x SOA interaction [$F_{(2,45)}$= 8.05 $p<0.001$] and a Drug x Relatedness x SOA interaction [$F_{(2,45)}$ = 3.31 $p<0.045$]. There was a 2-way Relatedness x SOA interaction [$F_{(2,45)}$ = 24.09 $p<0.001$] and a main effect of Relatedness [$F_{(1, 45)}$ = 4.82 $p<0.033$], with related pairs responded to faster (mean = 685.16 ± 121.66) than unrelated pairs (mean = 701.80 ± 120.37) There was also a main effect of Frequency [$F_{(1, 46)}$ = 13.77 $p<0.001$], with faster reaction times for high-frequency (mean = 680.22 ± 121.73) than low-frequency (706.74 ± 116.05) words. There was also a trend for a main effect of Drug (p= 0.093; Group means - 200ng/ml ketamine: 748.37±118.28; 100ng/ml ketamine: 670.67±111.12; placebo: 666.26±114.54).

	RT	Placebo	100ng/ml ketamine	200ng/ml ketamine	Polydrug Controls	Ketamine Users
Short SOA	High Related	646.7 (115)	644.2 (132)	718 (177)	659.4 (126)	621.3 (89)
	High Unrelated	667.4 (105)	673.1 (100)	735.8 (132)	683.7 (122)	660.0 (89)
	Low Related	644.6 (94)	652.4 (109)	734.7 (123)	660.7 (120)	642.6 (95)
	Low Unrelated	702.2 (153)	685.4 (113)	806.5 (153)	707.5 (131)	688.8 (91)
Long SOA	High Related	627.9 (107)	668.6 (86)	759.7 (158)	685.1 (115)	614.3 (79)
	High Unrelated	642.5 (120)	674.0 (93)	734.8 (123)	678.7 (114)	637.3 (77)
	Low Related	685.6 (123)	697.5 (107)	761.7 (118)	708.6 (139)	693.2 (92)
	Low Unrelated	713.3 (138)	680.4 (93)	736.0 (109)	745.8 (136)	662.2(85)

Abbreviations RT= reaction time, SOA = stimulus onset asynchrony

Table 4.2: Mean (SD) semantic priming RT's (in msecs) across SOA, frequency and relatedness (with associated priming effects) across participants in both Experiment 1 and Experiment 2

To explain the Drug x SOA x Relatedness interaction, we performed oneway ANOVAs using priming effects with the short SOA data; there were no group differences. There was a significant difference, however, at the long SOA [$F_{(2,45)} = 4.41$ $p=0.018$]. As can be seen from Figure 4.2, this reflects a ketamine effect with greatest priming effect in the placebo group, and lowest in the high-dose ketamine group. This effect was

confirmed by a significant linear trend across the 3 groups after the appropriate contrast [$t_{(45)} = 2.41$, $p<0.02$].

To further investigate the above interaction the raw RTs for related targets and unrelated targets were analysed, we did not find a significant Drug x SOA interaction in either analysis.

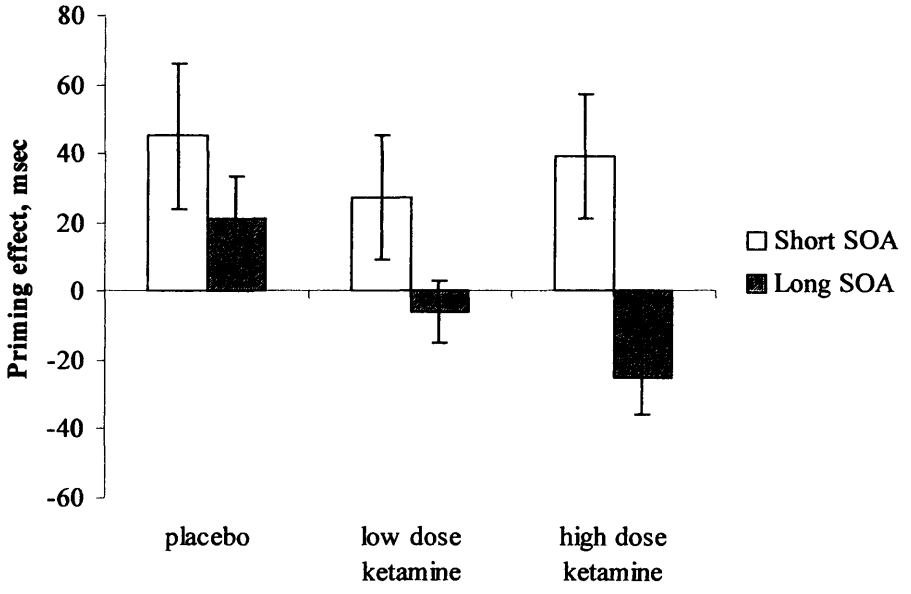


Figure 4.2: Priming (unrelated RT – related RT) scores across the 3 drug groups in Experiment 1 (placebo, 100ng/ml ketamine, 200ng/ml ketamine) and stimulus onset asynchrony (SOA: long and short).

Error data

Accuracy data for the 3 groups in each condition are shown in Table 3. There were no significant effects of Drug or group wise interactions showing that the groups are well matched in terms of accuracy

	RT	Placebo	100ng/ml ketamine	200ng/ml ketamine	Polydrug Controls	Ketamine Users
Short SOA	High Related	0.96 (2.6)	3.59 (8.2)	2.15 (3.7)	2.41(4.64)	1.93 (5.96)
	Low Related	4.68 (5.9)	5.09 (5.6)	3.20 (5.1)	6.01 (6.09)	5.44 (9.19)
	High Unrelated	3.37 (4.3)	6.77 (6.4)	2.23 (4.1)	2.15 (4.20)	5.00 (6.66)
	Low Unrelated	5.13 (7.1)	5.14 (6.3)	6.41 (7.1)	6.88 (7.82)	6.21 (9.40)
Long SOA	High Related	2.78 (3.7)	2.45 (5.4)	2.45 (4.6)	1.85 (3.31)	4.13 (7.87)
	High Unrelated	1.38 (2.5)	1.18 (2.5)	1.34 (2.77)	0.44 (1.78)	2.92 (8.42)
	Low Related	2.53 (4.2)	4.03 (6.1)	2.70 (5.55)	0.44 (1.78)	2.92 (8.42)
	Low Unrelated	2.57 (4.3)	3.19 (4.5)	2.23 (4.11)	0.52 (2.08)	3.18 (10.52)

Abbreviations RT= reaction time, SOA = stimulus onset asynchrony

Table 4.3: Mean (SD) semantic priming error data (in number of errors) across SOA, frequency and relatedness for Experiment 1 and Experiment 2.

4.4.3 Subjective Effects

4.4.3.1 SSQ

Schizotypal scores demonstrated a significant Drug x Time interaction [$F_{(2, 45)} = 4.03$ $p<0.025$]. Scheffe's test on change scores pre/ post demonstrated significantly higher schizotypal symptomatology scores between high-dose and placebo ($p<0.028$) [means

for change scores were (post - pre) : placebo –1.93±6.92; low-dose 1.67±6.95; high-dose 8.67±15.07].

4.4.3.2 ADDS

Dissociation scores showed a significant Drug x Time interaction [$F_{(2, 51)}$ = 7.12 $p<0.002$] and significant main effects of both Drug [$F_{(2, 45)}$ = 4.02 $p<0.026$] and Time [$F_{(1,45)}$ = 37.81 $p<0.001$] . Scheffe's test on change scores (post – pre) revealed significant higher dissociation scores in low-dose ($p<0.01$) and high-dose ($p<0.006$) ketamine group than placebo [mean change scores (post - pre) were placebo 1.07±3.30; low-dose13.4±11.04; high-dose 14.43±12.92)].

4.4.4 Correlations

There were no significant correlations between subjectively rated schizotypal or dissociative symptoms and priming effects.

Experiment 2 – Semantic priming in recreational ketamine users

4.5 Methods and Materials

4.5.1 Participants and Design

32 participants completed the study: 17 males and 15 females. As ketamine users are a population of 'poly-drug' users; the comparison group were poly-drug controls matched for other psychotropic drug use except ketamine. The age range was 19-45 years [polydrug controls: 21.50±3.20; ketamine group: 23.19±6.31]. Participants were recruited via volunteer databases, the internet and by snowball sampling (Solowij, Hall, and Lee, 1992). The ketamine group consisted of 16 participants who regularly took ketamine (a minimum of twice a month; 7 females). The control group consisted of 16 ketamine naïve participants who were broadly matched with ketamine users on recreational drug use apart from ketamine (8 females).

4.5.2 Procedure

All participants who met the relevant drug criteria provided written, witnessed, informed consent. An identical battery to that employed in Experiment 1 was used. Additionally, a general drug history was taken from the participant, detailing their current and past drug use. Participants were asked to give a urine sample to test for recent drug use (cannabis, MDMA, cocaine, opiates, ketamine and benzodiazepines).

4.5.3 Statistical Analysis

Statistical analyses were similar to those used in Experiment 1, except correlations were conducted between drug use and priming effects with the α levels raised to 0.01 to reduce type I errors.

4.6 Results

4.6.1 Demographics and Drug Use

There were no significant differences in age, gender or pre-morbid IQ [spot the word score- controls: 49.25±5.16; ketamine: 50.75±4.70]. Drug use data are presented in Table 4.4.There were no significant group differences in the use of cannabis, ecstasy or alcohol. The ketamine users had last used the drug a mean of 14.12±10.57 days ago, with a minimum last use of 3 days ago. Urine screens were all positive for cannabis but no other drugs of abuse. Other self-reported occasional drug use included cocaine (13 ketamine / 9 controls), amphetamines (10 / 2), benzodiazepines(2/1), LSD/ mushrooms (10 / 3), and amyl nitrate (4 / 0).

		Ketamine	Polydrug Controls
Ketamine	Days Per Month	4.44 (2.5)	0.00 (0.00)
	Years Used	2.02 (0.87)	0.00 (0.00)
	Amount Used Per Session (grams)	0.8 (0.57)	0.00 (0.00)
Cannabis	Days Per Month	9.31 (11.35)	11.00 (9.59)
	Years Used	4.69 (3.96)	5.25 (3.87)
	Amount Used Per Session (number of joints)	1.47 (1.38)	1.88 (1.10)
Ecstasy	Days Per Month	3.18 (3.47)	2.80 (4.78)
	Years Used	3.94 (3.03)	3.36 (3.07)
	Amount Used Per Session (tablets)	3.25 (2.29)	3.38 (4.66)
Alcohol	Days Per Month	13.69 (18.00)	14.94 (8.50)
	Years Used	8.88 (5.84)	6.38 (2.70)
	Amount Used Per Session (units)	6.00 (4.41)	7.00 (4.24)

Table 4.4: Mean (s.d.) of ketamine, cannabis, ecstasy and alcohol used by participants in the ketamine and control groups in Experiment 2.

4.6.2 Semantic Priming Task

Reaction Time Data

A 2x2x2x2 repeated measures ANOVA with Group (polydrug controls and ketamine), Frequency (high and low), SOAs (short and long), and Relatedness (related and unrelated pairs) was conducted using the reaction time data. These data are presented in Table 2. There was a 4-way Group x Relatedness x Frequency x SOA interaction [$F_{(2,30)} = 5.429$, $p = 0.027$], a 3-way Group x Relatedness x Frequency interaction [$F_{(2,30)} = 4.745$, $p = 0.037$], and a 2-way Relatedness x SOA interaction [$F_{(1,30)} = 8.17$, $p = 0.008$]. There was a main effect of Relatedness [$F_{(1,30)} = 30.99$, $p < 0.001$], whereby all participants were faster to respond to related (mean = 660.61 ± 97.64) than unrelated (mean = 682.97± 99.19) words, and a main effect of Frequency [$F_{(1,30)} = 30.99$, p

<0.001] where reaction times were quicker for high (654.92± 95.43) than low (688.67± 100.92) frequency words. There were no main effects of SOA or Group.

Priming effects (unrelated – related RT) were calculated and analysed. There was a 3-way interaction of Group x SOA x Frequency [$F_{(1, 30)} = 5.43$ $p<0.027$]; a 2-way Group x Frequency interaction [$F_{(1, 30)} = 4.75$ $p<0.037$] with greater priming effects in the ketamine group for high-frequency words compared to the poly-drug controls where the inverse pattern was evident (mean high-frequency - ketamine: 27.01±12.05, polydrug control: 9.09±12.42; low-frequency – ketamine: 14.27±11.38, poly-drug controls: 42.00±15.37); and a main effect of frequency [$F_{(1,30)} = 8.17$ $p<0.008$]. The 3-way interaction is depicted in Figure 3. Post-hoc multiple comparisons (oneway ANOVAs) revealed significant differences between the groups only for low-frequency words at a long SOA [F(1,30) =6.711 $p<0.015$], where the ketamine group exhibited significantly less priming than the poly-drug controls.

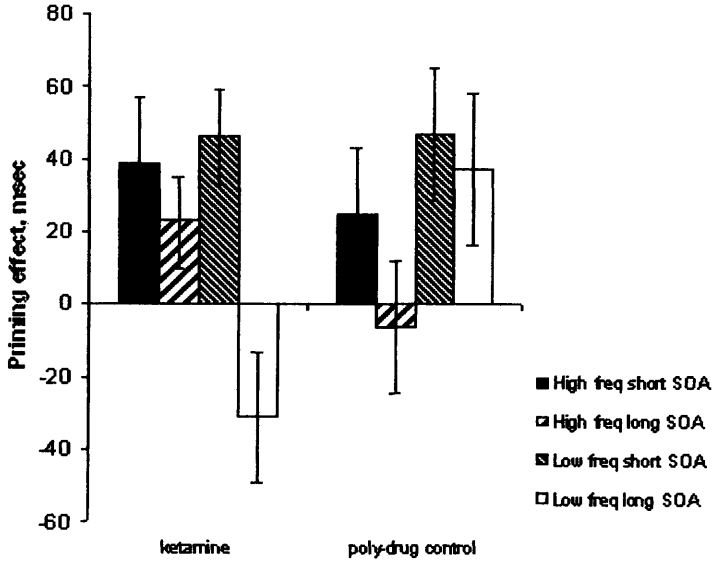


Figure 4.3: Priming (unrelated RT - related RT) scores across SOA and frequency in ketamine users and poly-drug controls in Experiment 2.

Error Data

The error data is displayed in Table 4.3. There was no main effect of group or group-wise interactions, thus establishing accuracy was well-matched across the groups.

4.6.3 Subjective Ratings

There were no significant group differences on any of the subjective measures of schizotypal and dissociative symptoms. (See Table 4.5)

4.6.4 Correlations

There was a trend, after Bonferroni correction, for a significant correlation in the ketamine group between days per month of ketamine use and the high-frequency/short SOA priming effect (r=0.511, p=0.043).

	Ketamine	Polydrug Controls
ADSS	8.20 (10.54)	6.81 (6.50)
PDI	35.13 (4.75)	34.50 (4.75)
SSQ	16.87 (9.90)	15.1 (11.25)
MRS: Sedation	51.00 (12.30)	49.78 (10.48)
MRS: Discontentedness	36.04 (16.41)	23.71 (26.24)
MRS: Anxiety	33.53 (14.20)	32.20 (15.`47)
Cognitive symptoms	45.50 (61.51)	55.38 (67.06)
Perceptual symptoms	44.69 (58.23)	47.43 (63.63)
Somatic symptoms	71.25 (50.53)	52.78 (59.44)

Table 4.5: Mean (SD) Subjective Effects in the ketamine and polydrug control groups.

4.7 Discussion

The current study set out to examine semantic priming following both acute and chronic ketamine. In Experiment 1, acute ketamine produced dose-dependent 'inverse priming', i.e. a suggestion of faster RTs to unrelated than related words, at the long but not the short SOA. Ketamine also produced increases in subjectively rated

schizophrenic and dissociative symptoms. In Experiment 2, the ketamine users also showed 'inverse priming' at the long SOA and not the short, but this time more specifically for low and not high frequency words. There were no other differences in priming between the groups. The groups did not differ in their drug use apart from ketamine and they were also well-matched on demographic variables and premorbid IQ. There was no evidence of any group differences in schizotypal, subjective or dissociative symptoms.

4.7.1 Acute ketamine

The key finding from Experiment 1 was that acute administration of ketamine produces a dose-dependent impairment of semantic priming at a long SOA. This was in accordance with our hypotheses and is, to our knowledge, the first study that has found a selective inverse priming effect at a long SOA with any group of subjects.

As discussed in the introduction three processes may be involved in semantic priming: automatic spreading of activation, expectancy and semantic matching. The only one of these processes to occur post-lexically is semantic matching i.e. matching primes and targets for semantic similarity. In terms of this data, ketamine may result in the semantic relationship between words being processed abnormally, resulting in slower RTs to related words than when semantic matching is intact. The disruption of controlled processing, i.e. semantic matching by ketamine is consistent with our original hypothesis. Previous research suggests that automatic processes are relatively preserved following acute administration of the drug (Chapter 2; Morgan et al., 2004a). Further work is necessary to tease apart the exact mechanisms involved in this impairment e.g. varying the strength of semantic association between word pairs to examine the role of semantic matching.

The reduction in priming observed here is somewhat similar to that seen in Alzheimer's disease (Giffard et al., 2002) following extensive damage to the semantic network. It would appear the administration of ketamine, potentially via its action at the

NMDA-receptor, acts as a massive insult to the semantic system. Ketamine may disrupt strategic semantic processing and this disruption is manifested as an inverse priming effect. The dose-related nature of the inverse priming effect at a long SOA, indicates a relationship between glutamatergic activity at the NMDA-receptor and the priming occurring at this time interval.

The N400 evoked related potential component is thought to reflect integration of stimulus meaning into an unfolding context (Kutas & Federmeier, 2000). This negative ERP component is normally attentuated in semantic priming paradigms but the attentuation of the N400 is reduced in cases of abnormal priming, e.g. with schizophrenics, whilst performing the task (Condray et al., 2003) and is also reduced after an acute dose of ketamine (Grunwald et al., 1999). This suggests that the ketamine-induced inverse priming observed in Experiment 1 may be the result of a deficit in online contextual processing of semantic information. NMDA-receptors have been proposed, via cognitive co-ordination, to play a role in contextual processing (Phillips and Silverstein, 2003). As semantic associations are probably dependent on contextual interactions (Kay et al., 1998) then disruption to NMDA-receptor activity could result in an inability to process contextual relationships between stimuli. One could speculate that a deficit in contextual processing would in turn lead to impaired semantic matching.

It is important to note that neither analysis of raw RTs for the unrelated and related words alone found an interaction of ketamine with SOA. Therefore it may be not only to decreased priming for related words but also facilitation of processing of unrelated words at the long SOA that are contributing to the interaction. Whilst the data from this study cannot speak to this issue, this topic is worthy of further investigation.

As predicted, an acute dose of ketamine did not differentially effect priming for high and low frequency words. Based on the aphasia literature (Warrington, 1975), the lack of frequency effects on semantic priming following acute ketamine suggest that the inverse priming finding reported earlier is the result of problems accessing semantic

knowledge and not problems with storage of semantic information, as one would expect following the acute administration of a drug.

The ketamine-induced impairment in semantic priming also suggests that the reduction in words generated on category fluency tasks observed in previous ketamine challenge studies are, in part, as a result of semantic memory deficits and not simply a by-product of impairments to other cognitive systems. These deficits may also contribute to ketamine-induced concreteness in proverb interpretation (e.g. Krystal et al., 1994). Given the lack of impairment at the short SOA, another potential explanation of these findings and the reduced number of words generated on the category fluency task could be an impairment in the efficiency of general semantic retrieval processes, which would be consistent with the lack of errors on this task. It may be that retrieval of one word serves to inhibit the retrieval of others. Studies using competition priming following an acute dose of ketamine may help to elucidate this point.

Limitations of Experiment 1 were that, despite the absence of a main effect of group overall, there were longer RTs in the group administered the higher dose of ketamine. These likely reflect the global sedative properties of this drug. Future studies might consider use of a sedative active placebo with minimal cognitive effects such as diphenhydramine. In Experiment 1 higher plasma levels of ketamine were achieved than targeted. However, variations in the plasma levels of ketamine achieved with this program have been found previously (e.g. Hetem et al., 2000) and may reflect inevitable individual differences in drug metabolism.

4.7.2 Chronic Ketamine

The main priming differences between ketamine users and poly-drug controls were of inverse priming selectively for low-frequency words at the long SOA. This probably reflects the combination of two processes. Firstly, inverse priming at the long SOA suggests an impairment in controlled processes as anticipated, and the probable reasons

for this have been discussed above. This was similar, yet not as profound, as that observed in Experiment 1.

Secondly, the impairment of priming for low-frequency words may signify degradation of the semantic store, as has been shown in the neuropsychological literature (Warrington & Shallice, 1979). Frequency differences may only be evident at a long SOA as they are not as marked as those seen in patients with semantic dementia. This is also further indication that automatic processing is relatively preserved. However, it maybe that heavier ketamine users would also show inverse priming at the short SOA. The findings of inverse priming for low-frequency words at a long SOA therefore concur with our hypothesis that chronic ketamine causes a degradation of the semantic store and accord with the findings on fluency reported in Chapter 5.

A limitation of Experiment 2 was in that in order to isolate ketamine effects in a poly-drug using population, it was necessary to compare ketamine users with poly-drug controls. The poly-drug control groups exhibited lower priming for high-frequency words at the long SOA than the placebo controls in Experiment 1. These differences in priming for high-frequency words at the long SOA may be a function of the poly-drug control group's use of other drugs, including ecstasy and cannabis. Previous work has examined the effect of pharmacological manipulations on semantic priming, using dopaminergic (L-dopa – Kishka et al., 1996; d-methampethamine – Gouzoulis-Mayfrank et al., 1998) and serotonergic (Gouzoulis-Mayfrank et al., 1998b; Spitzer et al., 1996) manipulations but these studies have failed to find effects on direct priming as examined in this study. However these studies did find effects on an indirect priming task, where instead of using directly related semantic pairs (e.g. lemon-sour), mediated semantic pairs are presented (e.g. lemon - sweet) which do not display the mediator (i.e. sour). Future work could also examine the effect of ketamine on both direct and indirect priming, as indirect semantic priming has been found, in some studies, to be a better indicator of impaired performance in schizophrenia (Moritz et al., 2001). Another inevitable limitation of recreational drug user research is that it is impossible to rule out pre-existing differences between the ketamine users and poly-drug controls without the

use of prospective studies. Therefore it may not be ketamine *per se*, that is accounting for these findings but underlying variation which pre-disposes people to ketamine abuse. Recent research has demonstrated that healthy individuals with a family history of alcohol abuse have a blunted response to ketamine (Petrakis et al., 2004). We did not take family histories from drug users in this study or examine genetic data but these issues should be addressed in future research.

Our findings add to the existing literature that suggests that repeated ketamine use produces chronic effects on semantic memory. It extends our original findings of a deficit in category fluency when ketamine users were drug free (3 days after use of ketamine), to suggest a longer term deficit that could be reflect a degradation of the semantic store. It would be interesting to investigate whether this degradation is reversible. Recent work has suggested that category fluency impairments are reduced when users substantially reduce their ketamine use (Chapter 5) but this could be a result of subtle changes in executive function or attention.

The acute administration of ketamine produced schizophrenia-like and dissociative symptoms. Although ketamine users did not differ from the poly-drug control group on schizophrenia-like symptoms, both groups scored similarly to healthy volunteers following the highest dose of ketamine given in Experiment 1. However, as the scale used to examine schizophrenia-like symptoms was adapted from a schizotypal trait scale, these scores may reflect the elevated schizotypy scores noted in drug users (Morizot & Le Blanc, 2003).

The differences between priming following a single dose of ketamine in drug-naïve volunteers and repeated doses of ketamine in recreational users have worrying implications for the growing population of ketamine users, in that they imply some degradation of the semantic memory store. In this respect, compared to healthy volunteers given acute dose of ketamine, ketamine users show a pattern of priming more similar to that observed in schizophrenics, where a degradation of the store has also been suggested (Rossell et al., 2000; 2004). However, it is not clear whether this

semantic degeneration is progressive with the course of the illness as there has been little work examining priming in first episode, unmedicated patients or in longitudinal studies. Therefore it could be that acute ketamine may better model aspects of the more acute phases of schizophrenia.

Accuracy in both Experiment 1 and Experiment 2 was generally good, which is a reflection of the subtlety of the semantic impairments we have observed. In addition, ketamine users did not have longer RTs overall. This suggests that repeated ketamine use has an impact on semantic organisation independent of psychomotor speed which is an important dissociation that is not present in schizophrenia or following acute ketamine, further highlighting the importance of using chronic ketamine 'modelling' to disentangle specific cognitive processes at work in schizophrenia.

In summary, this study found reduced priming at the long SOA following both acute and 'chronic' ketamine. This is indicative of strategic processing deficits and may possibly be mediated by NMDA-R effects on cognitive co-ordination. There was also inverse-priming for low-frequency words at the long SOA in the ketamine users compared to poly-drug controls. These two findings potentially indicate a gradual degradation of the semantic store. In conclusion, acute and chronic ketamine have differential, and yet in both cases detrimental, effects on semantic priming.

Chapter 5: Beyond the K-hole

A 3 year longitudinal investigation of the cognitive and subjective effects of ketamine, in recreational users who have substantially reduced their use of the drug

Question (CJAM): "What do you think are the negative long-term effects of ketamine use?"
Answer (Participant 10) "Well... that you end up locked inside your own head, beating your brain with a fish."

5.1 Overview

Ketamine is a dissociative anaesthetic that is also a drug of abuse. Previous studies have demonstrated persisting episodic and semantic memory impairments in recreational ketamine users 3 days after taking ketamine. However, it was not known the degree to which these deficits might be reversible upon reduction or cessation of ketamine use. This study set out to follow-up a population of ketamine users tested 3 years previously and examine whether impairments observed 3 days after drug use are enduring or reversible. 18 ketamine users and 10 poly-drug controls from studies conducted between 3 and 4 years earlier were re-tested on the same battery of cognitive tasks and subjective measures. These tapped episodic, semantic and working memory and executive and attentional functioning. Subjective schizotypal, dissociative, mood and bodily symptoms were also examined and a drug use history recorded. *Results:* The ketamine users had reduced their frequency of use of ketamine by an average of 88.3%. Performance of ketamine users on tasks tapping semantic memory had improved and this improvement was correlated with their reduction in ketamine use. On tasks tapping episodic memory and attentional functioning, ketamine users still showed deficits compared to poly-drug controls. Higher levels of schizotypal symptoms and perceptual

distortions were exhibited by the ketamine group although dissociative symptoms were similar to controls. These findings indicate that semantic memory impairments associated with recreational ketamine are reversible upon marked reduction of use, however impairments to episodic memory and possibly attentional functioning appear long-lasting. In addition, schizotypal symptoms and perceptual distortions may persist after cessation of ketamine use. Ketamine users, or potential users, should be aware of the enduring effects of this drug on aspects of memory and subjective experience.

5.2 Introduction

Ketamine is controlled under the Medicine's Act (1984) in the U.K. and other European Countries, whereas it is a scheduled drug in the U.S.. Estimates of prevalence of ketamine use are scant, however, in a survey of club-goers in the U.K., 10% stated that they took ketamine on a regular basis (Mixmag, 2002). In the U.S., emergency room visits associated with ketamine use have risen 2 000% between 1995 and 2002 (DAWN, 2003). Ketamine users report feelings of dissociation, hallucinations and out-of body experiences as the effects that draw them to use of the drug (Siegel, 1978). Indeed, the reinforcing effects of acute ketamine have recently been demonstrated in a controlled laboratory study of healthy volunteers. We (Chapter 6; Morgan et al., 2004b) found that non-drug abusers liked the effects of the drug and desired more of it, especially at low doses.

As discussed in Chapter 1, ketamine has long been acknowledged to be a psychotomimetic drug (Domino, Chodoff, and Corssen, 1965) and as such has been extensively investigated in the laboratory (Krystal et al., 1994; Chapter 2; 6; Morgan et al 2004a; 2004b; Newcomer et al. 1999). The psychotomimetic properties of ketamine have lead to the development of the NMDA-hypofunction model of schizophrenia (Olney et al., 1999), which may have implications for psychopharmacological treatments for this disorder. However, there have been some suggestions that the acute effects of NMDA-antagonism may not be as appropriate a model of schizophrenia as the chronic effects (Jentsch & Roth, 1999). This assertion has been supported largely by animal work (Jenstch et al. 2000) but is also implied in the human phencyclidine (PCP) literature. PCP is a non-competitive NMDA-antagonist similar to ketamine but with a ten-fold greater affinity for this receptor (Rainey & Crowder, 1974). There was a high incidence of PCP abuse, especially in the United States, in the 1970's and 1980's. Anecdotally, there were many reports of protracted PCP psychosis following chronic use lasting several days (Ellison, 1995). Whilst it is difficult to estimate the proportion of PCP users who developed psychosis from clinical reports, one study examined 1 000

patients presenting in emergency rooms with PCP intoxication. Twenty-five percent of this sample developed psychotic or catatonic reactions persisting for longer than the duration of acute drug effects (Allen & Young, 1978).

Despite the potential of chronic ketamine administration to induce a state resembling aspects of schizophrenia, there has been little research examining the consequences of its repeated use in the burgeoning population of users. Three studies have examined the effects of ketamine on the night of drug use and then 3 days later when drug free (Curran & Morgan, 2000; Curran & Monaghan, 2001; Chapter 3; Morgan et al., 2004d). The effects on the night of drug use, in all 3 studies, were similar to those observed following an acute dose in the laboratory with healthy volunteers. But it was also found that, when compared to poly-drug using controls, three days after drug use ketamine users were still impaired on tasks tapping episodic and semantic memory (Curran & Morgan, 2000). In addition, they scored more highly on scale assessing schizotypal and dissociative symptoms. Using a 'source' memory task, in Chapter 3 we reported findings that replicate the day 3 episodic memory impairments. We also revealed these deficits to be selective, in that ketamine users could say whether they had seen a word previously (correct item recognition) but could not remember the context in which it had been presented (impaired source memory). This is a similar pattern of episodic memory impairment to that observed in schizophrenia (Danion, Rizzo, and Bruant, 1999) but intriguingly this is not observed following an acute dose of ketamine in the laboratory (Chapter 6). Curran & Monaghan (2001) compared frequent and infrequent ketamine users on day 3. They found greater impairments on episodic and semantic memory tasks in frequent ketamine users compared to infrequent users three days after taking the drug.

These day 3 effects can be interpreted in three ways (Curran & Morgan, 2000). Firstly, it is possible that these were residual effects of ketamine use. However, this interpretation is not sufficient to account for the data for several reasons. Firstly, residual impairments would theoretically have been observed in both infrequent and frequent users, however this was not the case. Secondly, subsequent research with

healthy volunteers following an acute dose of ketamine has found no evidence of residual effects of ketamine 3 days following an acute dose (Chapter6; Morgan et al., 2004a). Finally drugs acting on the glutamatergic NMDA-receptor affect fast excitatory synaptic potential change and the elimination half-life of ketamine is 2-3 hours (Goodman & Gilman, 2001), thus it is unlikely it would still be affecting behaviour 3 days after use. The second explanation is that these are chronic effects, possibly related to neurotoxicity which is observed in animals following repeated doses of NMDA-receptor antagonists (e.g. Ellison, 1995) . The third explanation was that these are pre-existing differences between ketamine users and non-users. Whilst it is difficult to rule out the possibility of pre-existing differences without prospective studies, the ketamine users were well matched with poly-drug controls on education, IQ and other demographic variables and were drawn from the same social group. The explanation of these day 3 deficits in terms of chronic effects thus appears most plausible. However, the central question remains as to the mechanism underlying these chronic effects of ketamine and whether it is possible to recover these functions upon cessation of ketamine use. In monkeys, self-administered PCP for up to 8 years did not produce any adverse physical reactions (Carroll, 1990). However in rats, studies that have administered single or highly spaced repeated doses of NMDA-receptor antagonists have found neurotoxicity that is localised mainly in cingulate and retrosplenial cortices (Olney et al. 1989; Olney et al. 1991). Also in rats, 5 days of continuous PCP treatment led to a different, more prolific pattern of neurodegeneration in a number of limbic system and limbic–related structures including the hippocampal and entorhinal cortices, the posterior cingulate cortex and olfactory regions (Ellison, 1995). Given most ketamine users are prone to bingeing and repeated dosing over an evening or a few consecutive days it is possible that the latter pattern of neurotoxicity is more relevant to their drug use.

No study has yet examined the effects of reduction of ketamine use on cognition and memory in humans. One study did investigate the effects of reducing phencyclidine (PCP) use in 15 PCP-users (Cosgrove & Newell, 1991) compared to 15 poly-drug controls. This work reports an initial impairment in PCP users (compared to poly-drug

controls) that reversed upon cessation or reduction of PCP use over 4 weeks. However, the findings of this study are difficult to interpret as little information is given on the degree of reduction in drug use and the potential relationship between this and recovery of cognitive function. Also, no data on the degree to which poly-drug users were matched with controls were presented. Further, the subjects were tested only over a 4-week period when they were taking other drugs concurrently. Finally, cognitively there were few significant differences at baseline or follow-up between poly-drug and PCP users, these only emerged when the data was collapsed into an 'impairment ratio' measure, which is of unknown validity. Thus, there is currently no existing research that adequately addresses the question of whether chronic effects of NMDA-receptor antagonists are reversible upon reduction or cessation of use of this drug.

Therefore the current study intended to investigate, using a longitudinal design, the impact of cessation or reduction of use of ketamine in a population of drug users tested between 3 and 4 years previously in two previous studies (Curran and Morgan et al., 2000; Curran and Monaghan, 2001). The longitudinal design allows for examination of the extent to which changes in cognitive measures are due to changes in ketamine use. By comparing again to poly-drug controls, if cognitive impairments are chronic and yet reversible the performance in abstinent ketamine users should improve on episodic and semantic memory tasks to similar levels as poly-drug controls. However if impairments observed three days after drug use in the original studies were due to pre-existing differences or permanent chronic effects then performance should not differ from that on day 3 in the original study.

5.3 Method

5.3.1 Design

An independent group, longitudinal follow-up design was used. Data from day 3, when participants were drug free, were used for comparison with follow-up data and will hereafter be termed 'baseline data'. Originally participants were recruited from night-clubs and parties via snowball sampling (Solowij et al., 1992) and expressed an interest

in taking part in future work. Attempts were made to contact these original participants. It was possible to contact 33 of the original 76. Thirty-one wished to take part in the follow-up study, which included 19 of the original ketamine users. However, one member of the original ketamine group had subsequently developed schizophrenia and 2 of the poly-drug controls had started using ketamine. These volunteers were therefore excluded, leaving 18 participants from the original ketamine group and 10 from the original poly-drug control group.

5.3.2 Procedure

On the testing day participants were given a volunteer information sheet and then asked to give written, witnessed, informed consent. The participants gave details of their current drug use and answered some questions about their patterns of ketamine use (i.e. craving, periods of abstinence etc.). Premorbid IQ was assessed using the Spot the Word test (Baddeley et al., 1993) which requires participants to make lexical decisions between pairs of words and non-words. They were then assessed on a battery of cognitive tests.

5.3.3 Test Battery

The same battery of tests used as in the two previous studies was employed to compare data across time points. Tests were originally selected to assess memory functions, related cognitive functions, dissociative and psychotogenic symptoms. Test versions were initially counterbalanced across participants and design, and participants received different versions to those they received 3 or 4 years previously.

Semantic Memory

Speed of Comprehension (Baddeley et al., 1992) – Participants were presented with 200 sentences some of which were semantically correct (e.g. 'Sharks are good swimmers') and some of which were not (e.g. 'Wives are made in factories'). Participants were then instructed to go through the sentences for two minutes marking

with a tick those which were semantically correct and, with a cross, those which were not. Scores were in number of correctly judged sentences and number of errors.

Semantic (Category) Fluency - Participants were provided with a super-ordinate category member (e.g. fruit) and asked to generate as many members of that category as possible in 90 seconds. The number of correct exemplars and number of repetition (i.e. perseverative errors: PE) and category (i.e. semantic errors: SE) errors were recorded.

Episodic Memory

Prose Recall – Participants were played a taped passage of prose from the Rivermead Behavioural Memory Battery (Wilson et al., 1985) and were asked to recall it immediately afterwards and then after a delay, filled with other tasks, of approximately 20 minutes. Recall was scored in terms of 'idea units' recalled, with one point for each exact synonym and half a point for incomplete recall or a close synonym (maximum score is 21).

Executive functioning

Digit Cancellation task – Participants were asked to delete all the instances of the digit '4' from a sheet containing 400 random numbers. This task tapped focussed attention. Scores were time taken to complete the task and errors of commission/ omission.

Serial Sevens Task – Participants were asked to sequentially subtract seven from a three figure number as many times as they can in a 90 second period. This task taps working memory. The number of correct subtractions and errors were recorded.

Phonological (Verbal) Fluency - Participants were given a single letter prompt (e.g. R) and required to generate as many words beginning with that letter in 90 seconds. This task was used a simple index of frontal functioning. Scores were number of correct exemplars and errors of repetition (i.e. perseverative) and alphabetical errors.

Subjective Rating Scales

The following subjective rating scales were administered to participants: SSQ, ADDS, MRS, SES and are decribed in Chapter 2. Additionally we administered the Hospital Anxiety and Depression Scale (HADS) -A 14-tem questionnaire which was used to assess anxiety (HADS-A) and depression (HADS-D). Participants were asked to rate their mood "over the last week".

5.3.4 Statistical Analysis

All statistical analyses were performed using SPSS Version 10.0. Repeated measures analyses of variance (RMANOVA) were conducted using time (3/4 years ago or current) as the within-subject variable and drug condition (ketamine user or polydrug control) as the between subject variable. When RMANOVA drug x time interactions were significant then post-hoc t-tests were conducted. For non-parametric data Mann-Whitney U was used and dichotomous data was analysed using χ^2 analyses. Correlations were conducted using Pearson's correlation coefficient for parametric and Spearman's rank order correlation for non-parametric data. Correlations were only conducted on measures with significant group effects or interactions to minimise the chance of Type 1 errors. Correlations were conducted between ketamine, cannabis and alcohol use and performance on the cognitive measures and schizophrenic-like symptoms. Correlations were also only conducted with the ketamine group, to avoid replicating group differences. Non-signficant main effects and interactions are not reported.

5.4 Results

5.4.1 Demographics

There were 28 participants in total included in the study, 18 ketamine users (4 females) and 10 polydrug controls (6 females). There were no group differences in age or premorbid IQ as assessed with the Spot the Word test. There were no differences in anxiety as indexed by the HADS, between the ketamine users and poly-drug controls.

However poly-drug controls scored less than ketamine users on the HADS depression scale (U=55.5, p<0.031). Data are given below in Table 5.1.

	Age, years	Spot the Word, no. correct	HADS-A	HADS-D
Ketamine Users	28.1 (0.81)	48.38 (3.46)	7.89 (4.96)	5.27 (4.32) *
Polydrug Controls	26.5 (0.70)	50.12 (3.16)	6.63 (3.74)	2.00 (2.45)

* p<0.05

Table 5.1: Demographic variables and standard deviations across groups.

5.4.2 Drug Use (Table 5.2)

There were no differences in the proportion of each group that rated themselves as regular users of cannabis, alcohol, cocaine or ecstasy when examined with a χ^2. In addition, there were no differences between the groups in the number of days per month they used these drugs. Dose data was not analysed due to difficulties in standardising participants estimates of drug use. There was a trend indicating the ketamine group had used cannabis for a longer number of years than controls (U= 46.5, p=0.052), this mirrored the non-significant age difference between the groups. There were no other differences in length of regular use of drugs.

Other current drug use reported by participants included amphetamines (4 ketamine users, 1 control), benzodiazepines (1 ketamine user, 1 control), LSD/psilocybin (2 ketamine users, 1 control).

Ketamine users had decreased their frequency of ketamine use by an average of 88.3%, with 8 not having used the drug for over 6 months. The ketamine group used the drug a mean of 1.61 (3.19) days per month compared to a previous mean frequency of 6.45 (8.13) days per month at baseline. Whilst the number of days the ketamine was used

had decreased, the mean dose of ketamine used had increased from 0.31 (0.25) grams at baseline to 0.44 (0.97) grams at follow-up.

	Ketamine	Control
Percentage regular cannabis users	77.8%	80%
Days per month cannabis used	14.56 (2.91)	12.30 (4.05)
Years since cannabis first used	9.94 (5.94)	8.37 (5.77)
Percentage regular alcohol users	94.4%	100%
Days per month alcohol used	16.67 (2.69)	13.70 (3.23)
Years since alcohol used	12.59 (4.37)	12.53 (3.83)
Percentage regular MDMA users	72.2%	60%
Days per month MDMA used	1.36 (0.35)	1.10 (0.41)
Year since MDMA first used	6.53 (3.74)	5.96 (3.64)
Percentage regular cocaine users	61.1%	50%
Days per month cocaine used	2.28 (0.94)	1.00 (0.44)
Years since first cocaine first used	3.35 (4.24)	2.89 (3.80)

Table 5.2: Drug use and standard deviations in ketamine and poly-drug control groups

5.4.3 Cognitive Tasks

5.4.3.1 Category generation (Figure 5.1)

A significant group x time interaction emerged on the number of category members generated ($F_{1,26} = 5.19$, p=0.032) and a main effect of time ($F_{1,26} = 7.50$, p=0.011). Simple effects revealed that this was due to significantly lower numbers of category members generated by the ketamine users at original testing on day 3 ($t_{1,27} = 2.42$ p=0.023) but no difference between the groups 3 years later. There was a main effect of group ($F_{1,26} = 6.13$, p=0.02) on the number of perseverative errors , indicating more

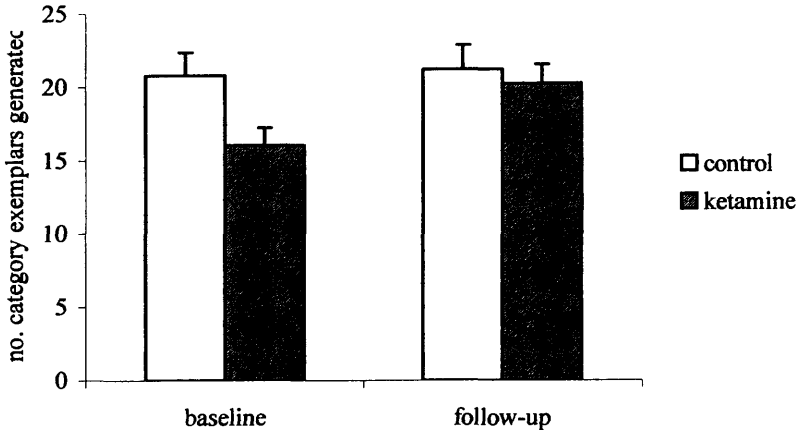


Figure 5.1: Number of category exemplars generated in category fluency task in ketamine and poly-drug control users at baseline and follow-up.

PE were made by the ketamine group than controls at both time points (Table 5.4). Semantic errors were at floor levels in both groups at follow-up.

5.3.4.2 Speed of Comprehension Task

A significant main effect of group was found on this task ($F_{1,26} = 8.73$, $p=0.007$). The ketamine group completed fewer sentences on both test sessions than controls. But, as can be seen from Figure 5.2, the number of sentences judged correctly appears to increase in the ketamine group between day 3 and the 3 year follow-up testing point. Analysis of errors on the speed of comprehension task yielded a significant interaction ($F_{1,26} = 4.35$, $p=0.047$). Simple effects analysis demonstrated that this was due to a significant difference between the groups on day 3 but not at follow-up. However, as can be seen from Table 5.3, errors were at floor at follow-up.

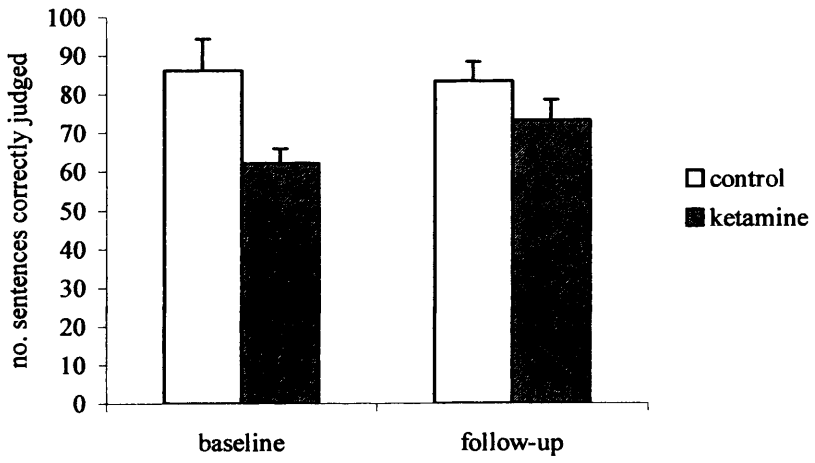


Figure 5.2: Number of sentences correctly judged in the speed of comprehension task in ketamine and poly-drug control users at baseline and follow-up.

5.4.3.3 Prose Recall

Immediate prose recall scores showed a significant main effect of group ($F_{1,26} = 4.36$, $p=0.047$) reflecting better recall in the control group on both the original testing occasion and at follow-up (Figure 5.3a). Delayed prose recall reflected a similar pattern of results with a significant main effect of group ($F_{1,26} = 4.43$, $p=0.045$). Again, from Figure 5.3b, a reduction in memory performance in the controls is visible, however the main effect reflects a tendency for the ketamine group to perform worse overall.

5.4.3.4 Digit Cancellation

There was a significant main effect of group on digit cancellation scores ($F_{1,26} = 7.09$, $p=0.013$) but no interaction or main effect of time. This represents a poorer performance by the ketamine users over both time points [mean baseline 66.01 (14.12)

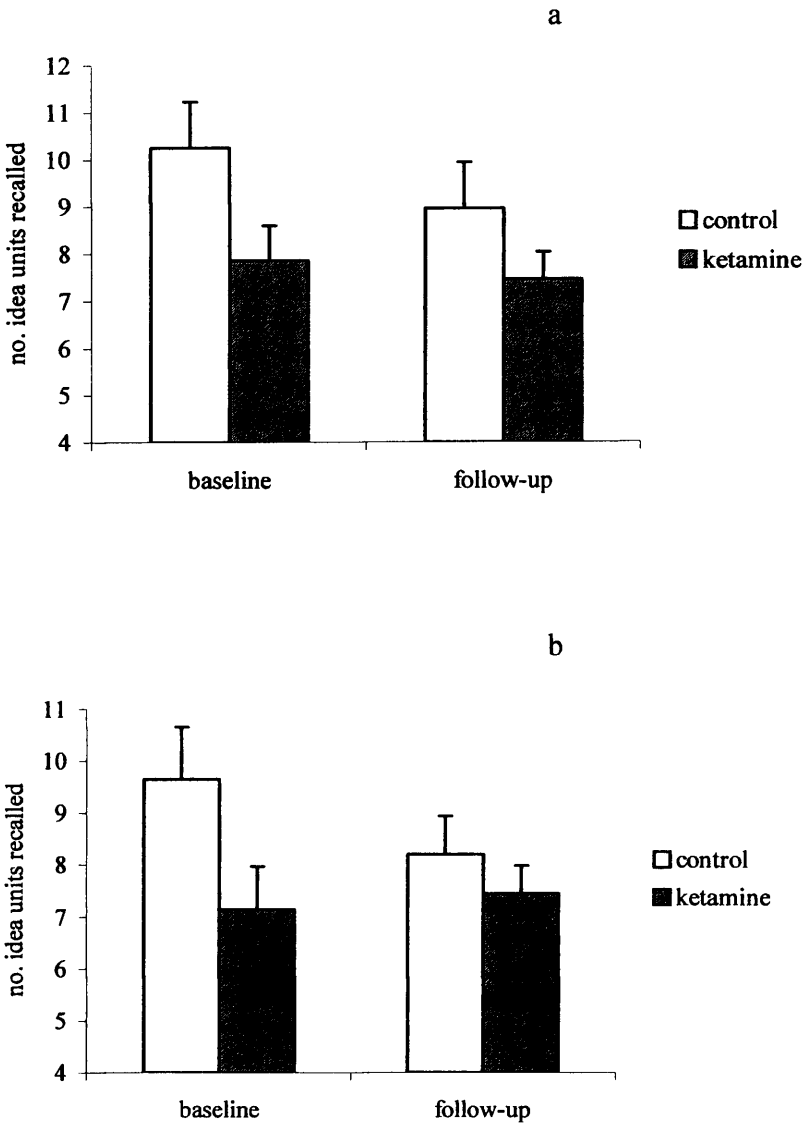


Figure 5.3a: Immediate and 5.3b delayed prose recall scores across group and testing point, bars represent SEM.

secs, follow-up 65.32 (11.34) secs] compared to controls [mean baseline 54.60 (7.82) secs, follow-up 55.97 (8.74) secs]. There were no differences in the number of errors made (Table 5.3). Covarying digit cancellation time for errors did not affect the outcome of the analysis.

	Baseline		Follow-up	
	Ketamine	Control	Ketamine	Control
Category fluency, PE	1.94 (2.36)	0.5 (0.71) *	1.29 (2.29)	0.4 (0.68) *
Speed of comprehension, errors	1.06 (1.12)	0.2 (0.42) *	0.38 (0.46)	0.4 (0.52)
Digit cancellation, omission errors	1.06 (1.10)	0.5 (0.53)	1.5 (1.47)	1.1 (1.37)
Verbal fluency, PE	2.0 (1.41)	1.0 (0.94)	1.06 (1.76)	0.6 (0.84)
Serial Sevens, errors	3.78 (5.46)	2.2 (3.19)	0.9 (1.28)	1.5 (1.94)

* $p<0.05$

Table 5.3: Error rates and standard deviations across all tasks at baseline and follow-up testing in ketamine users and controls, PE = perseverative errors

5.4.3.5 Serial Seven's and Verbal fluency

There were no significant differences between controls and ketamine users at either time point on verbal fluency [baseline mean ketamine :19.8 (6.23) words, controls: 21.00 (5.94) words; follow-up ketamine 21 (5.62) words, controls 20.4 (4.01) words] or the serial seven's task [baseline mean ketamine : 24.8 (8.16) subtractions, controls: 20.78 (10.17) subtractions; follow-up ketamine 22 (9.33) subtractions, controls 23 (7.97) subtractions] . There was a trend for a main effect of group on number of perseverative errors on the verbal fluency task ($F_{1,26} = 3.30$, $p=0.081$) and a main effect of time ($F_{1,26} = 3.17$, $p=0.087$). This reflected poorer performance overall in the ketamine group, and poorer performance at follow-up than baseline in both groups.

5.4.4 Subjective Measures (Table 5.4)

5.4.4.1 Schizotypal Symptomatology Questionnaire

There was a significant main effect of group ($F_{1,26} = 15.32$, $p=0.001$) and of day ($F_{1,26} = 59.25$, $p<0.001$) but no interaction. The ketamine group still exhibited a greater

degree of schizotypal symptomatology than the control group, however there was a decrease in schizotypal scores in both groups over the 3 or 4 years.

5.4.4.2 Adapted Dissociative States Scale

There was a significant main effect of time on the ADDS ($F_{1,26} = 5.93$, $p=0.022$) which reflected a decrease in scores on the dissociative scale in both groups.

5.4.4.3 Mood Rating Scale

There were no group differences on any of the three factors of the mood rating scale (Drowsiness, Discontentedness and Anxiety) across the time points.

5.4.4.4 Subjective Effects Scale

The subjective effects can be divided into 3 factors : bodily, perceptual and mental state/cognitive. There were significant differences between the control group and ketamine users at follow-up on all three of these factors: perceptual distortions ($U=34$, $p=0.007$); bodily symptoms ($U=21$, $p=0.001$); and cognitive and mental state ($U=39.5$, $p=0.014$). These differences all reflected higher scores in the ketamine users than the controls.

5.4.5 Correlations

A highly significant correlation was found between change (Follow-up score – baseline score) in category fluency and both change in ketamine use ($r = 0.712$, $p<0.002$) and time since last ketamine use ($r= 0.723$, $p<0.002$). To investigate whether impaired performance on the digit cancellation task might have resulted in significantly impaired performance on other tasks , correlations between digit cancellation at time 3 and immediate and delayed recall were conducted. No significant correlations emerged.

	Baseline		Follow-up	
	Ketamine	Control	Ketamine	Controls
SSQ total	51.5 (21.28)	24.8 (8.16) **	18.67 (17.05)	4.0 (4.06) *
ADSS total	10.11(15.38)	5.44 (5.85)	3.24 (4.53)	0.80 (1.54)
MRS-Sedation	24.64(17.87)	38.55 (20.67)	37.07(17.18)	33.84(19.66)
MRS – Dis-contentedness	21.47 (14.5)	37.92 (9.59) **	34.3 (19.55)	31.48 (23.12)
MRS- Calm	24.54 (13.87)	37.9 (9.59) *	36.61 (21.23)	39.85 (23.08)
BSS- somatic	12.12 (12.61	9.62 (16.58)	9.33 (7.14)	1.14 (1.25) **
BSS – perceptual	13.43 (9.20)	1.12 (1.56)	8.4 (7.71)	1.18 (1.45) **
BSS-cognitive	16.13 (20.08)	14.00 (20.08)	14.47 (14.89)	3.75 (3.95) *

* $p<0.05$, ** $p< 0.01$

Table 5.4: Subjective effects and standard deviations across groups at baseline and follow-up

5.5 Discussion

This study set out to investigate whether cognitive impairments observed 3 days after ketamine use in recreational drug users were reversible upon cessation or reduction of use of the drug. There were two main findings of this study. Firstly, ketamine users demonstrated a recovery of semantic memory function which was highly correlated with their reduction in use of the drug. Secondly, there was some evidence of a persisting impairment in episodic memory. Additionally, there was evidence of an attentional deficit after cessation or reduction of ketamine use. Decreases in dissociative and schizotypal symptomatology were found across both groups, however schizotypal symptomatology remained higher overall in the ketamine group compared to poly-drug controls.

The results of the current study suggest that upon reduction of ketamine use it is possible for ketamine users to recover some aspects of semantic memory function. The ketamine group showed a marked impairment of category fluency at baseline (day 3) compared to poly-drug controls. They generated fewer category exemplars when given a superordinate category name. In addition, they verified less sentences as semantically correct and made more errors of judgement on the speed of comprehension task. The two groups were well-matched on drug use, IQ and age, thus these differences appear to be attributable to ketamine use. Furthermore, deficits in performance on category fluency and speed of comprehension tasks were not found in healthy volunteers 3 days after a single dose of ketamine (Chapter 6; Morgan et al., 2004c). This suggests that these decrements in recreational users are not residual but chronic effects of ketamine.

But by follow-up testing 3 years later, aspects of semantic memory function had recovered. The number of exemplars generated on the category fluency task was no longer different from that of the poly-drug controls. On the speed of comprehension task, over both time points, the ketamine group judged less sentences correctly. However, ketamine users did improve on the number of sentences they judged correctly between day 3 and follow-up testing. The ketamine group also made a similar number of errors on the speed of comprehension task as the poly-drug controls at follow-up, which again suggests a recovery of semantic memory function. Three years after original testing, the ketamine group made more errors on the category fluency task, however as these were perseverative errors, they may be indicative of an executive functioning, rather than a semantic memory, deficit.

Amongst drugs of abuse, ketamine is unique in its capacity to impair semantic memory (Curran & Weingartner, 2002). This effect appears to be more pronounced in ketamine users than in healthy volunteers given a single dose of ketamine, where data on semantic memory deficits are equivocal (Adler et al., 1998; Krystal et al., 1994; Malhotra et al., 1996; Chapter 2; Morgan et al., 2004a). Semantic memory impairments were further elucidated in Chapter 4, however we were unable to use this task in the

current study as we were confined to the use of the measures from the original study. The semantic memory impairment associated with ketamine abuse is somewhat reminiscent of schizophrenia. Of the diverse cognitive deficits within the broad category we label " schizophrenia", category fluency has been suggested to be the most robust neuropsychological indicator (Arango et al., 1999). It is possible that the ketamine induced category fluency deficits are mediated in a similar way to those observed in schizophrenia, given the psychotomimetic properties of ketamine. The schizophrenia literature suggests that an impairment of category fluency could reflect one of two problems with semantic memory, either an impairment of access/ retrieval or a disorganisation of the semantic store (Allen et al., 1993). In this study, there were no baseline impairments in verbal fluency in ketamine users compared to poly-drug controls. If category fluency deficits reflect an impairment of access/retrieval from semantic memory then theoretically both verbal fluency and category fluency may have been equally impaired. The selective impairment to category fluency observed in the current study is therefore suggestive of a ketamine-induced disorganisation of the semantic store. This would appear to be, at least partially, reversible upon reduction of ketamine use. The latter assertion is supported by the high correlation between reduction in ketamine use and improvement in category fluency.

The number of sentences correctly judged on the speed of comprehension task improved in ketamine users but was still lower than that of controls. Unfortunately, as we used no measures of general reaction time it is not possible to tell the degree to which the lower number of sentences judged is reflective of general psychomotor slowing or semantic impairment. However, the reduction in number of errors observed made again suggests semantic memory improvement.

The neural substrates of this reversible impairment in semantic memory are unclear. Animal studies with NMDA-antagonists have demonstrated diffuse neurotoxicity throughout the brain following repeated doses of NMDA-antagonists. In rats, neurotoxicty in the posterior cingulate cortex (retrosplenial cortex) was found to be reversible 48 hours following an acute dose of an NMDA-antagonist (Olney et al.,

1991). This area has been demonstrated to be important in semantic memory in humans (Nestor et al., 2002). However, it is difficult to extrapolate from this animal literature and to speculate as to what may be occurring neurologically to produce this improvement in functioning in ketamine users. Two neuroimaging studies of chronic PCP users compared to controls have suggested reduced glucose utilisation in prefrontal areas (Hertzman et al., 2002; Wu et al., 1991). As intact performance on fluency tasks is dependent upon the integrity of the prefrontal cortex, this may account for the initial impairments observed in ketamine users and recovery of pre-frontal function may underpin the reversal of deficits with markedly reduced ketamine use. Imaging studies would help to elucidate the neuroanatomical substrates of these impairments.

Episodic memory functioning in ketamine users did not appear to recover after reduction in use of the drug. At baseline, ketamine users recalled less of a passage of prose than poly-drug controls and at follow-up their performance level on prose recall was similar to baseline. This apparently persisting impairment was not correlated with the attention deficits observed on digit cancellation. As the groups were well matched on drug use, this deficit could be either attributable to pre-existing differences or ketamine use. The study reported in Chapter 3 demonstrated that ketamine users exhibit a selective impairment to source, and not recognition memory (Morgan et al., 2004b). It is not possible to tell from the present data if the persisting impairment in episodic memory observed here reflects a deficit in source memory, item memory or a generalised episodic memory impairment. Given the literature on source memory impairments in schizophrenia, it would be important to tease apart the nature of this episodic memory deficit.

This deficit may be related to ketamine induced neurotoxicity. A recent study that have administered repeated doses of ketamine to rats for 5 consecutive days and then examined neuronal functioning 3 weeks later, observed abnormal neurogenesis in the hippocampus, an area important in human episodic memory (Bernstein et al., 2003). It may be that similar abnormal neurogenesis occurs in humans who have repeatedly self-

administered the drug, but further work is necessary to clarify this issue. Given the high densities of NMDA-receptors in areas important in memory in humans, it is feasible that repeated NMDA-antagonism could produce non-reversible impairments in episodic memory.

This group of ketamine users were slower at completing the attentional task both at baseline and follow-up. This was surprising as in the previous study, compared to poly-drug controls, there had been no evidence of an attentional impairment in ketamine users (Curran & Morgan, 2000). The combined ketamine user group in this study used the drug more heavily than the ketamine group reported in the latter study. In addition, those participants from the study by Curran & Monaghan (2001) exhibited poorer attentional functioning at baseline than the ketamine users from the Curran & Morgan (2000) study. Thus heavy ketamine use appears to be associated with attentional impairments. This finding is intriguing as an acute dose of ketamine in the laboratory has been repeatedly associated with preserved attentional functioning (Krystal et al., 1994; Malhotra et al., 1996; Adler et al., 1998; Newcomer et al., 1999; Chapter 2 /Morgan et al., 2004a). However, there have been some suggestions of impaired vigilance following acute ketamine (Hetem et al., 2000; Krystal et al., 2000b). Ketamine users have reported attentional impairments to be a perceived long-term side effect of ketamine use (Siegel, 1978) and the findings of this study could be taken as evidence in support of these subjective reports. However, there was no difference in the number of errors made between the groups. Thus the slower digit cancellation time could again be indicative more general psychomotor slowing and not an attentional impairment, per se. Covarying for errors did not affect the outcome of the analysis so these findings would not appear to be attributable to a speed/accuracy trade off on the part of the controls.

Working memory and aspects of frontal functioning tapped by the serial seven's and verbal fluency tasks were preserved both on day 3 and at follow-up, compared to controls. There was a trend for an increase in perseverative errors in the ketamine group at both time points. This warrants further investigation, given the perseverative errors

observed on the category fluency task. These errors could well reflect problems monitoring and holding 'on-line' exemplars that have been generated in fluency tasks. The serial seven's task requires a lower level of maintenance in working memory than fluency tasks, but a higher level of manipulation. It could be that ketamine users have impaired maintenance, but intact manipulation of material in working memory.

Ketamine users exhibited higher levels of schizotypal symptoms and rated themselves more highly on visual analogue scales of perceptual distortions (e.g. visual, auditory, time perception and out of body experiences), cognitive impairments (e.g. impaired memory and concentration; confusion) and physical effects associated with ketamine (e.g. dizziness, bodily numbness, lack of co-ordination). Schizotypal symptoms had declined 3 years after initial testing but were still higher than controls. Schizotypal symptoms had also decreased in the poly-drug control group. This could be related to the documented reduction in schizotypy with increasing age (Morizot & Le Blanc, 2003). It is not clear whether these elevated scores on schizotypal scales reflect pre-exisiting differences or chronic effects of ketamine use. No correlation was found between schizotypal symptoms and ketamine use. The scale used in this study was adapted to index state, rather than trait, schizotypy and reliably demonstrates change following acute ketamine. Nevertheless it remains possible that the scale was tapping into underlying schizotypal traits. Equally, however, the finding of increased schizotypal scores could be taken as evidence supporting the argument that chronic ketamine may be model some of the symptoms of schizophrenia. Whilst only anecdotal evidence, it is also interesting to note that one of the ketamine users from the sample of 19 had developed schizophrenia. This has never been reported in longitudinal studies of other recreational drug using populations (e.g. ecstasy and cannabis users, (Zakzanis & Young, 2001).

Ketamine users also scored more highly than controls on visual analogue scales of subjective effects including physical, perceptual and cognitive factors. They perceived themselves amongst other symptoms to be more confused, have impaired memory and concentration, rated themselves as more dizzy, and as experiencing a variety of

perceptual phenomena including visual and auditory distortions. These could again be chronic effects of ketamine use and warrant further investigation. There were no differences in dissociation overall, but dissociative scores reduced in both groups across time. This may again be related to an increase in age and changes in lifestyle.

The longitudinal follow-up design used in this study was useful in allowing comparison across the groups over a 3-4 year time period. None of the volunteers had escalated use or even continued at the same level and all reported having little problems reducing their ketamine use, indicating a low potential for dependence on this drug. Unfortunately though, it was not possible to contact many of this population due to their transient lifestyles, as many were 'squatters' and 'travellers'. Potentially, the 38 members of the original ketamine group that could not be contacted may have continued ketamine use. In terms of experimental design, ideally a 'continuing ketamine' group would have been studied, as it is possible that other factors have caused the current sample to reduce their use. It is also impossible to rule out pre-existing differences between ketamine users and non-ketamine using poly-drug controls without the use of prospective studies. But groups were well matched on other drug use and demographic variables. Moreover, the ketamine group's scores on category fluency, at follow-up, were similar to those observed in the poly-drug using controls which does not suggest pre-existing differences in at least semantic memory functioning. Again, if a greater number than 2 participants in the poly-drug control group had started using ketamine, then examining the performance of a group of these type of drug users would have shed further light upon this issue. There were also differences between the groups on the HADS measure of depression at follow-up. Clinical levels of depression may impact on performance on attention and episodic memory tasks but there is no evidence to suggest that it would have affected semantic memory function (Zakzanis et al., 1998) and our ketamine users were not within a clinical range of depression. Nevertheless, the finding of increased depression is interesting, as ketamine has been reported to have prolonged antidepressant properties in depressed patients (Berman et al., 2000). Unfortunately, it was not possible to compare across the two studies on this measure as Curran & Monaghan (2001) did not

report the HADS, however participants in Curran & Morgan (2000) did not differ from controls on depression at baseline.

The present study also had several limitations in common with virtually all studies of recreational drug users (Curran, 2000). Retrospective estimates of drug use are inevitably inaccurate and it was not possible to investigate the participants' reports objectively. It is also difficult to tease apart the effects of different drugs and their interactive effects on cognition in a population of poly-drug users. However, the high correlations with reported drug use and differing objective cognitive measures give some indication of which effects are attributable to which drug.

In summary, this study used a longitudinal, follow-up design to compare ketamine users and poly-drug controls scores from 3 days after taking the drug, with their performance 3 years later when all had ceased or reduced using the drug. Attentional impairments and schizotypal symptoms remained greater than those of poly-drug controls between 3 days and 3 years, however there was some decline in schizotypal symptoms in both groups across the two testing points. There was also evidence of an impairment in episodic memory that was still evident after 3 years. Semantic memory function was found to be impaired on the category fluency and speed of comprehension tests on day 3 but 3 years later category fluency performance and errors on the speed of comprehension task did not differ from controls. This indicates some recovery of semantic memory performance, but speed of comprehension was still slower. The improvement in category fluency correlated with the reduction in use of ketamine. These findings support the notion that repeated doses of ketamine may model aspects of schizophrenia. Whilst users may recover some cognitive function following cessation of ketamine use, ratings of subjective effects in ketamine users suggest that they may still experience some of the symptoms associated with the use of the drug up to 3 years afterward.

Chapter 6: Special K?

Ketamine impairs response inhibition and is positively reinforcing in healthy volunteers: a dose response study

"A major concern for the safe use of Ketamine is its very high potential for psychological addiction. A very large percentage of those who try Ketamine will consume it non-stop until their supply is exhausted. I've seen this in friends I've known for many years who are regular psychedelic users and never had problems controlling their drug use..."

D M Turner (1994), The Essential Psychedelic Guide

6.1 Overview

The present study aimed to investigate the effects of ketamine on two processes related to drug abuse, response inhibition and reinforcement, and to examine whether an acute dose of ketamine produced residual cognitive effects in healthy volunteers. 54 healthy volunteers were given an 80 minute infusion of one of two doses (0.4, 0.8 mg kg^{-1}) of ketamine or placebo. Subjects carried out a battery of tests at three time points: pre-infusion, during the infusion and 3 days later at follow-up. The battery consisted of tests of episodic and semantic memory, schizophrenic-like and dissociative symptoms, response inhibition and measures of subjective effects, including mood, bodily symptoms and enjoyment of and desire for the drug. Ketamine acutely impaired response inhibition and had related biphasic effects on the subjective reinforcing effects of the drug. Ketamine also acutely impaired episodic but not semantic memory and increased schizophrenic-like and dissociative symptoms. No residual cognitive effects were observed 3 days following an acute dose. The reported increasing abuse of ketamine may be related to its capacity both to reinforce and to decrease response inhibition. The lack of residual effects in healthy volunteers on day 3 indicate that impairments found on day 3 in ketamine abusers suggests chronic effects in ketamine abusers. Although pre-existing differences cannot be ruled out, ketamine is a drug with high abuse potential and the consequences of its continued abuse may be severe.

6.2 Introduction

Despite the increasing rate of ketamine abuse, little research has examined the effects of ketamine in relation to its reinforcing or dependence forming properties. Ketamine is self-administered in rats and non-human primates (Winger et al., 1989; Marquis et al., 1989) and in rats, produces conditioned place preference (Layer et al., 1993). Various processes are thought to underlie the maintenance of drug abuse. These include variations in dopaminergic transmission (Di Chiara, 1999) and more recently disruptions to other neurotransmitter systems have been implicated, including glutamate (Cornish et al., 1993). In humans, the role of cognitive processes in drug abuse and addiction, alongside neurotransmitter modulation, has been also emphasised (Giancola, 2000; Weingartner, 2000). Impaired executive functioning, that is the planning, initiation, and self-regulation of goal-directed behaviour, is related to increased drug use and likelihood of developing a substance use disorder (Giancola et al., 1996). Of the executive functions, it is inhibitory processes that are thought to be particularly important in models of drug abuse (Goldstein & Volkow, 2002). In relation to response inhibition, acute doses of ketamine have been demonstrated to disrupt performance on tasks in which defective inhibitory mechanisms are implicated, i.e. the Wisconsin Card Sorting Task (WCST) (Krystal et al., 1994; 1997; 2000). However, no research to date has directly examined processes of response inhibition following ketamine

Only two studies have examined the effects of ketamine in recreational users of the drug, these have been discussed previously in the thesis but as they are the basis of our rationale, they will also be reviewed here. A previous study set out to examine the acute and residual effects of ketamine in a population of abusers (Curran & Morgan, 2000). This compared volunteers who reported taking ketamine with a population matched for poly-drug use, on the night of their ketamine use (day 0) and three days later (day 3). Day 0 effects replicated previous laboratory acute studies showing a broad range of cognitive impairments (e.g. Krystal et al., 1994). Interestingly however, three days later, participants were still impaired on tasks tapping episodic and semantic memory, and had elevated levels of dissociation and

schizotypal symptoms. The authors proposed three interpretations of this data. Firstly that regular use of ketamine over time may produce chronic effects. This may be related to animal studies suggesting that a single high dose or repeated doses of NMDA-antagonists may destroy neurons in the posterior cingulate and retrosplenial cortices and several other corticolimbic brain regions (Olney et al., 1991). Secondly, that ketamine may produce more transient residual impairments on these tasks that, given the short-half life of ketamine, may possibly be attributable to the action of norketamine, a metabolite of ketamine with suggested psychotomimetic properties. Finally, that there are pre-existing differences between ketamine users and non-users that account for these day 3 effects.

In an attempt to clarify the former interpretation, a study compared both frequent and in-frequent users of ketamine using a similar design, thus controlling for residual effects in both groups and reducing the possibility of pre-existing differences causing preference for ketamine use (Curran & Monaghan, 2001). Episodic and semantic memory impairments observed on day 3 in the previous study were found in frequent but not infrequent ketamine users. This does suggest chronic effects of ketamine, as more transient residual impairments would theoretically have been observed in both the groups. However, it is possible that had the infrequent user group been compared to poly-drug controls then residual impairments may have still been evident. Thus, it is not clear whether the findings reflect a residual effect, possibly attributable to higher dose, a chronic effect of repeated ketamine use or a combination of the two. If the results of these studies do indeed represent a residual effect of ketamine, then impairments should be observed in healthy volunteers with no history of ketamine abuse. If no residual effect of ketamine is found in healthy volunteers then we can infer that the residual impairments seen in previous studies were likely due to either chronic repeated use of this drug or to pre-existing differences between ketamine abusers and poly-drug controls. One previous study (Newcomer et al., 1999) examined residual schizophrenic symptoms in healthy volunteers 48 hours after an infusion and found no evidence of residual effects. However, this study did not assess residual cognitive effects which have been shown by both Curran & Morgan (2000) and Curran & Monaghan (2001).

Therefore the present study intended to investigate the acute and residual effects of a single dose of ketamine in healthy volunteers. Cognitive function was examined on measures which demonstrated residual impairments in recreational users. No previous study has examined the potential residual cognitive effects of ketamine in healthy volunteers, this would seem to be important, given evidence of residual effects in recreational users and suggestions of neurotoxicity in the animal research. In addition, as no research to date has investigated the effects of ketamine on measures related to drug abuse, this study set out to investigate the effects of ketamine on response inhibition and measures that tapped drug-related subjective effects, including the participant's liking of and desire for the drug.

6.3 Method

6.3.1 Design, Procedure and Participants

This exactly followed the method reported in Chapter 2. Thus on the main test day the 54 participants were randomly allocated to receive either ketamine (0.4 mg kg^{-1} or 0.8 mg kg^{-1}) or saline placebo (0.9% NaCl) intravenously for 80 minutes. This chapter reports further assessments on the main test day. Further all participants returned 4 days later for follow-up testing, lwhere they completed a similar battery of tests for residual effects and also gave a urine and peripheral venous blood sample.

6.3.2 Assessments

Tests were selected to assess response inhibition, semantic and episodic memory, dissociative and psychotogenic symptoms and subjective effects (including drug incentive salience). Additional tests were administered pre and post drug, the results of which have been reported in Chapter 2. Test versions were counterbalanced across participants and design.

Prose Recall sub-test of the Rivermead Behavioural Memory Test (Wilson et al., 1985) - This task was used to test immediate and delayed prose recall. Participants were played a pre-recorded passage of prose similar to a news bulletin on a tape recorder. They were then asked to state verbally as much as they could recall i) immediately after presentation and then ii) after a short delay, filled with other

tasks, of approximately 10 minutes. Participants were tested both pre and post drug on immediate and delayed recall. A third condition required participants to recall information learnt pre drug and information learnt post drug at the same time, after a long delay at the end of the infusion.. This was to assess whether ketamine impairs encoding (information learnt post drug should be more poorly remembered) or retrieval (both sets of information should be remembered equally as badly) in episodic memory. The passage of prose contained 21 'idea units'. Scoring was standard with each correctly remembered unit or exact synonym given one point, and half point scores were awarded for partial recall or partial synonyms.

Source Memory task – See Chapter 2 for details (only follow-up data are presented here)

Fluency - Semantic and phonological tasks were chosen to tap executive functioning and retrieval from semantic memory. In Semantic Fluency, participants were provided with a super-ordinate category member (fruit, vegetables, musical instruments) and asked to generate as many members of that category as possible in 90 seconds. Categories were matched for frequency of examples (Battig & Montague, 1969) In Phonological Fluency, participants were provided with a single letter prompt (R, M or B) and were required to generate as many words beginning with that letter in 90 seconds. Letters were matched for number of occurrences in the Oxford Mini-Dictionary (OUP, 1984). Number of category members and errors were recorded for both tasks.

The Hayling task (Burgess & Shallice, 1997) - This task was chosen to tap response initiation and response inhibition. In section one of the task, participants were read fifteen sentences each of which had the last word is missing (e.g. He posted a letter without a ...). The participant was asked to give a verbal response to complete the sentence, as quickly and sensibly as possible. In the second section of the test the participant is again presented with fifteen sentences but this time was asked to give a response that was completely incongruous with the sentence. The task yielded four measures, latency of response on section one (response initiation) and errors and latency to respond for the second section of the test (response suppression) along

with an overall test score. As there was only one version, this task was only administered post drug.

6.3.3 Subjective ratings: The SSQ, ADDS and MRS described in Chapter 2 were again administered on day 4. In addition, the SES was given at each time point. This VAS was designed to test subjective side-effects of ketamine administration. The SES had fifteen items: memory impairment, out-of body experiences, visual distortion, sound distortion, altered time perception, dizziness, impaired concentration, depression, feeling of altered reality, impaired memory, nausea or sickness, bodily numbness, unsteadiness, lack of co-ordination, confusion.

On the pre (as a control) and post-drug assessments, three additional items adapted from Kirk et al. (1998) were used to gauge the participant's attitude towards the drug. Participants were required to rate whether they felt the effects of a drug (scale anchored between 'Feel very strong effect of a drug' and 'Feel no effect of a drug'); whether they wanted more of the drug (scale anchored between 'Want more of the drug' and ' Want less of the drug') and whether they liked the effects of the drug (scale anchored between 'Like effects of the drug a lot' and ' Do not like the effects of the drug').

6.3.4 Statistical Analysis

All statistical analyses were performed using SPSS Version 9.0. Group differences were examined using one-way ANOVAs and, where data was non-parametric, the Kruskall-Wallis test. For most cognitive tasks and subjective effects 3 x 3 repeated measures analyses of variance (RMANOVA) were conducted using time (pre-drug, post-drug, follow-up) as the within-subject variable and drug condition (placebo, 0.4mg kg^{-1} ketamine , 0.8 mg kg^{-1} ketamine) as the between subject variable. Where significant interactions were found, orthogonal contrasts were conducted comparing 1) placebo with both drug groups and 2) low dose with high dose ketamine. Pearson's correlations were conducted on selected data. Throughout, assumptions of normality were examined using Levene's tests and Bonferroni corrections were applied, where appropriate, to control for multiple comparisons. Non-significant main effects and interactions are not reported.

6.4 Results

6.4.1 Trait Scores, Demographics and Drug dosage

Participants were broadly matched for age. Groups were additionally matched on premorbid I.Q. (as gauged by the 'spot the word' test), depression, anxiety, trait dissociation, millilitres (mls) infused and weight (Table 6.1). In total the 0.8 mg kg^{-1} group received a mean of 56.45± 9.19 mg ketamine over 80 min. The low dose group received 26.74 ± 7.56 mg ketamine over 80 mins (see Chapter 2 for further details).

	Placebo, mean (s.d)	0.4 mg kg^{-1} ketamine, mean (s.d)	0.8 mg kg^{-1} ketamine, mean (s.d)
Age	21.83 (3.15)	21.17 (1.69)	24.17 (4.53)
Spot the word test score	50.00 (3.20)	49.67 (3.65)	49.65 (3.87)
BDI score	3 (3.6)	4.3 (4.9)	3.5 (4.9)
STA score	34.6 (10.8)	32.5 (8.79)	33.8 (9.7)
DES score	32.3 (32.39)	31.6 (30.3)	31.5 (35.5)
Weight, kg	71.29 (13.92)	66.84 (18.87)	70.56 (11.49)
Mls infused	31.2 (6.05)	29.8 (3.71)	30.9 (5.58)

Table 6.1: Demographics across treatment groups

6.4.2 Cognitive Assessments

6.4.2.1 Prose Recall

A 3 x 2 x 2 RMANOVA of drug x test delay x time yielded a significant time x drug interaction [$F(2, 51) = 6.98$ $p<0.05$], a significant main effect of delay [$F(2, 102) = 88.22$ $p<0.001$] and time [$F(1, 51) = 4.37$ $p<0.05$]. Post-hoc analysis with Dunnett's t demonstrated higher recall scores overall post-drug in the placebo group than the high dose ketamine group ($p<0.005$) but no difference in scores between the two drug groups or any pre-drug differences. Analysis of the delay effect revealed significantly lower scores than immediate recall after a short delay across the groups and time points[$F(1,51) = 4.18$ $p<0.05$] and significant differences between scores after a short delay and scores after a long delay i.e. at the end of the infusion [$F(1,51) = 104.13$ $p<0.001$]. These effects and interaction can be seen in

the pre and post drug scores depicted in Figure 6.1. There were no differences in immediate and delayed prose recall scores at follow-up [group means immediate recall: Placebo:=10.92 ±2.73; low dose ketamine = 10.22±3.90; high dose ketamine = 9.13±3.51, group means delayed recall: Placebo = 10.47± 3.0; low dose ketamine = 9.72±3.603; high dose ketamine = 8.33±2.75]

6.4.2.2 Source Memory

A one-way ANOVA demonstrated no group differences on follow-up item recognition or source memory data.

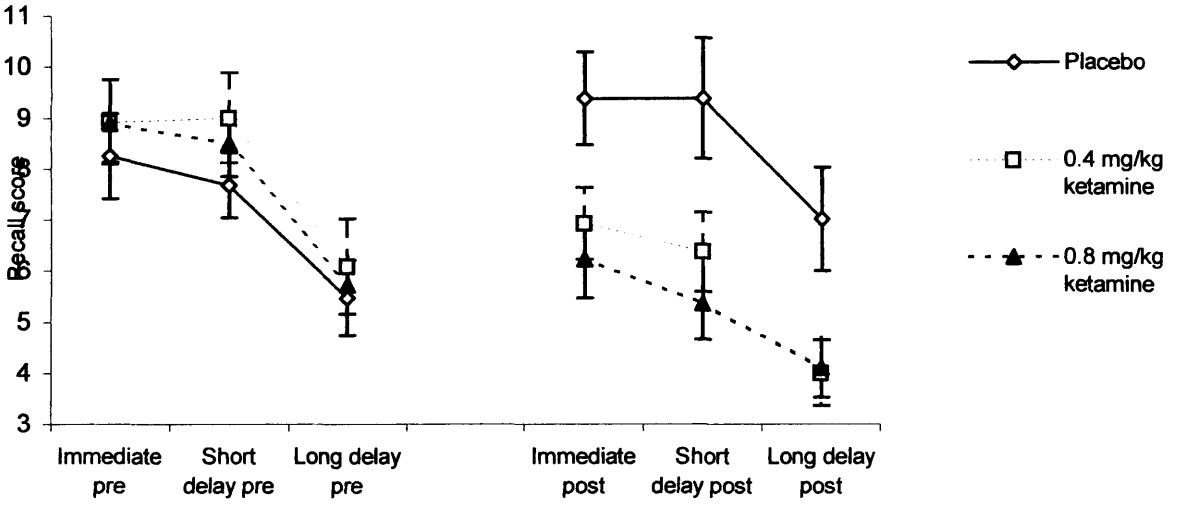


Figure 6.1: Prose recall scores pre and post drug across the three delay intervals and drug conditions

6.4.2.3 Fluency (Table 6. 2)

Phonemic Fluency

A RMANOVA showed a significant main effect of time on verbal fluency [F(2, 102) = 4.80 $p<0.05$ p=0.01], attributable to significantly lower scores post-infusion compared to follow-up [F (1, 51) = 11.68 $p<0.01$ p=0.001] but no main effect of drug or interaction.

Semantic Fluency : A repeated measures ANOVA revealed a significant main effect of time on category fluency [F(2, 102) = 5.72 $p<0.01$ p= 0.004] with significantly lower scores overall post infusion compared to pre-infusion [F(1,53)= 5.52 $p<0.05$

p=0.023] and follow-up [F(1, 53) = 9.65 p<0.01 p=0.003] but no interaction or main effect of drug.

6.4.2.4 The Hayling Task

Scores for the Hayling were computed and analyses performed on four scores I) time to complete Hayling part 1 (logical completion); II) time to complete Hayling part 2 (illogical completion); III) number of errors on Hayling part 2 (inability to suppress logical responses where not required / response inhibition); and V) overall Hayling test score. A RMANOVA of task (Hayling 1 or Hayling 2) x drug, yielded a significant main effect of task [F(1,51) = 96.44 p<0.001], but no interaction or main drug effect. All groups took longer to complete the Hayling 2 sentences. Analysis of Hayling part 2 errors revealed significant differences between the groups [F(2,53) = 10.30 p<0.001]. Contrasts found a difference between numbers of errors made in both ketamine groups and placebo [t(51) =2.67 p<0.02] which, as can be seen in Figure 2, was due to the 0.8 mg kg -1 ketamine group making more errors than the 0.4 mg kg -1 ketamine group [t(51) = 3.67 p<0.01].

In addition analysis of the overall Hayling test score found a significant difference between the drug treatment groups [F(2, 53) = 5.65 p<0.01]. Contrasts were used to examine this data further and showed significantly lower scores in the 0.8 mg kg -1

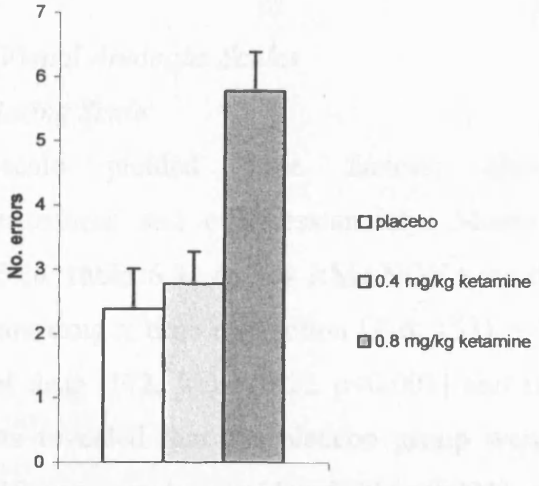


Figure 6.2: Number of response inhibition errors made on the Hayling task across drug conditions

ketamine group compared to the 0.4 mg kg -1 ketamine group[t(51) = 3.01 p<0.01] but no difference when both high and low drug groups were compared to placebo [means: placebo = 17.78 ± 2.10; low dose =17.94 ± 1.39; high dose = 15.67 ± 3.01].

6.4.3 Subjective Effects

6.4.3.1 Schizotypal Symptomatology

When the overall score for schizotypy was computed, RMANOVA demonstrated a significant drug x time interaction [F(4, 102) = 10.33 p<0.001] and a significant effect of time [F(2, 102) = 36.93 p<0.001]. Contrasts showed significant differences post drug, where the drug groups scored more highly than the placebo group [t(51)= 3.19 p<0.001] but there was no difference between the low and 0.8 mg kg -1 ketamine groups (Table 6.2).

6.4.3.2 Dissociative Symptomatology Scale

RMANOVA of the overall DSS score showed a significant drug x time interaction [F(4, 102) = 21.33 p<0.001] and significant main effects of drug [F(2, 51) = 15.23 p<0.001] and time [F(2,102) = 87.61 p<0.001]. Ketamine induced clear, dose-related dissociative effects. These were confirmed by further analysis of the interaction which revealed significantly lower scores in the placebo group compared to the two drug groups post-drug [t(51) = -5.76 p<0.001] and in the 0.4 mg kg -1 group compared to the 0.8 mg kg -1 ketamine group post-drug [t(51) = -3.16 p<0.01] (Table 6.2).

6.4.3.3 Visual Analogue Scales

Mood Rating Scale

This scale yielded three factors: alertness/drowsiness, contentedness/ discontentedness and calmness/anxiety. Means for the mood rating scale are reported in Table 6.3. A 3x4 RMANOVA of the factor ' drowsiness' yielded a significant drug x time interaction [F(6, 153) = 7.90 p<0.001] , a significant main effect of drug [F(2, 51) = 9.22 p<0.001] and time[F (3, 153) = 67.93 p<0.001]. Contrasts revealed that the placebo group were less drowsy than the two drug groups 10 min post drug [t(51)=-5.30 p<0.001], and 80 min post drug [t(51) = -6.19 p<0.001]. Analysis of the 'discontentedness' sub-factor yielded a significant drug x time interaction [F(6, 153) = 2.69 p<0.025] and significant effect of time [F(3, 153)

= 5.56 p<0.01].Contrasts indicated that the 0.8 mg kg -1 ketamine group were significantly more discontented 80 min post drug than the 0.4 mg kg -1 ketamine group (t(51)= -2.08 p<0.05]. There were no significant differences between any of the groups or assessment points on the 'anxiety' sub factor of the mood rating scale.

6.4.3.4 'Feel effects of a drug?'

There was a significant drug x time interaction for the VAS of 'feel effects of a drug' [F(4,102) = 27.38 p<0.001] and significant main effects of both time [F(2, 102) = 187.56 p<0.001] and drug [F(2, 51) = 55.68 p<0.001]. Tests of simple effects showed significant group differences 10 min [F(2, 53) = 33.55 p<0.001] and 80 min post drug [F(2, 53) = 50.71 p<0.001]. The 0.8 mg kg $^{-1}$ ketamine group felt stronger effects 10 min post drug than the 0.4 mg kg $^{-1}$ ketamine group [t(51) = -2.64 p<0.05 p=0.011] and both drug groups felt stronger drug effects than the placebo [t(51) = -7.75 p<0.001]. 80 min post drug there were no differences in two ketamine groups, but both groups felt much stronger effects than the placebo [t(51) = -9.99 p<0.001]. In Figure 6.3 the differences between the placebo group and the two drug groups can be clearly seen as the change is from 0 to 80/90mm of the100m m scale.

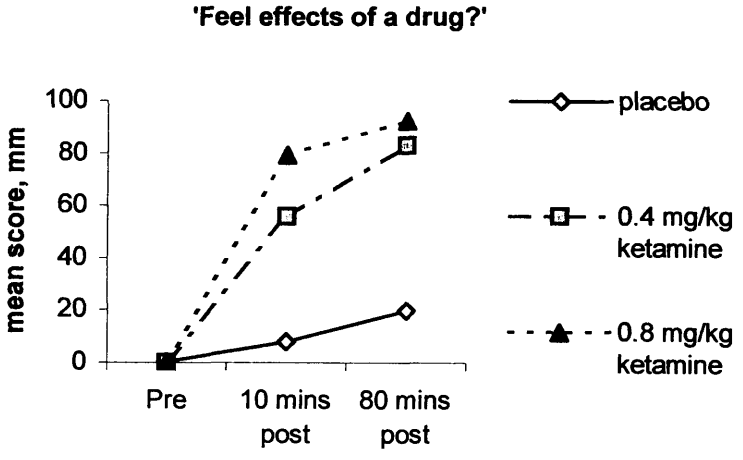


Figure 6.3: The subjective 'feeling' of drug effects on ketamine, across dose and time.

	Placebo			0.4 mg/kg ketamine			0.8 mg/kg ketamine		
	Pre	Post	Follow-up	Pre	Post	Folow-up	Pre	Post	Follow-up
Phonological fluency, N	14.56 (4.19)	14.38 (3.57)	15.89 (3.92)	15.11 (4.13)	15.33 (2.45)	16.39 (2.70)	15.33 (4.60)	13.72 (0.39)	16.17 (2.94)
Phonological fluency, errors	0.33 (0.59)	0.33 (0.49)	0.28 (0.57)	0.11 (0.32)	0.33 (0.59)	0.5 (0.86)	0.28 (0.46)	0.61 (0.85)	0.39 (0.50)
Semantic fluency, N	17.11 (4.57)	15.58 (3.92)	17.89 (4.80)	18.72 (4.32)	17.72 (3.71)	19.17 (3.85)	18.67 (4.01)	15.72 (4.23)	19.06 (4.25)
Semantic fluency, errors	0.44 (0.62)	0.33 (0.69)	0.17 (0.38)	0.44 (0.70)	0.06 (0.24)	0.22 (0.55)	0.33 (0.49)	0.67 (1.14)	0.22 (0.55)
Schizotypal symptoms	6.89 (10.64)	4.61 (4.49)	3.17 (3.97)	4.78 (6.80)	14.39 (14.56)	3.94 (6.35)	6.89 (10.40)	18.61 (9.99)	3.94 (6.86)
Dissociative states scale	1.00 (1.28)	2.33 (3.19)	0.28 (0.58)	1.06 (1.66)	15.28 (11.23)	0.72 (1.27)	1.06 (3.07)	27.27 (15.91)	3.17 (7.67)

Table 6.2: Group means (s.d) for scores on fluency, schizotypal and dissociative scales across each assessment point

6.4.3.5 'Like effects of the drug?'

For the rating 'like effects of the drug' there was a significant drug x time interaction [$F(4, 102) = 6.60$ $p<0.001$], and significant main effects of time [$F(2, 102) = 94.65$ $p<0.001$] and drug [$F(2,51) = 10.41$ $p<0.001$]. Tests of simple effects showed significant differences between the groups at 10 min [$F(2,53)= 11.39$ $p<0.001$] and 80 min post drug [$F(2, 53) = 6.44$ $p<0.01$]. At both time points the drug groups liked the 'effects of the drug' more than the placebo group, 10 min [$t(51) = -.469$ $p<0.001$], 80 min [$t(51) = -3.07$ $p<0.01$]. There was a trend for the 0.4 mg kg -1 ketamine group to like the effects of the drug more than the 0.8 mg kg -1 ketamine group at 80 min [$t(51) = 1.85$ $p=0.07$]. These effects are clearly observable in Figure 6.4 where at 10 min the drug groups rated their liking of the drug similarly but at 80 min the high dose ketamine group's ratings had decreased.

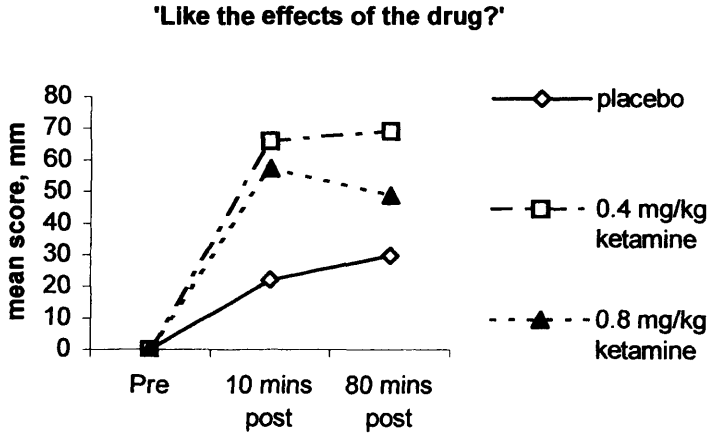


Figure 6.4: The subjective effects of ketamine on ratings of drug 'liking' across dose and time point.

6.4.3.6 'Want more of the drug?'

The visual analogue scale 'want more of the drug' yielded a significant drug x time interaction [$F(4, 102) = 4.92$ $p=0.001$], a main effect of time [$F(2, 102) = 63.47$ $p<0.001$] and drug [$F(2, 15) = 6.67$ $p<0.01$]. Both drug groups had similar 'wanting

more' ratings at 10 min, but at 80 min this desire had increased in the 0.4 mg kg $^{-1}$ group and decreased in the 0.8 mg kg $^{-1}$ ketamine group. These effects can be observed in Figure 6.5 and were reflected in further analysis. Simple effects revealed drug differences 10 min post drug [$F(2, 53) = 7.08$ $p<0.01$] and 80 min post drug [$F(2, 53)= 5.04$ $p<0.05$]. At 10 min post drug both of the drug groups wanted more of the drug than the placebo group [$t(51)= -3.72$ $p <0.001$] . At 80 min post drug the two drug groups again wanted more of the drug than the placebo group [$t(51) = -2.23$ $p<0.03$] but the 0.4 mg kg $^{-1}$ ketamine group in turn wanted more of the drug than the 0.8 mg kg $^{-1}$ ketamine group [$t(51) = 2.26$ $p<0.03$] .

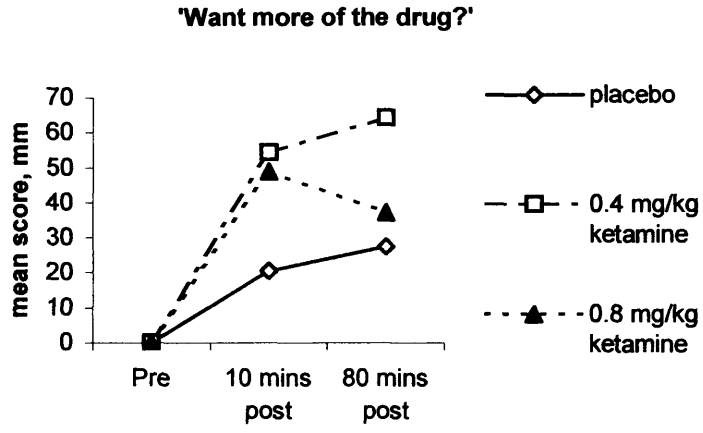


Figure 6.5: The subjective effects of ketamine on ratings of wanting more of the drug across dose and time point.

Subjective Effects Scale (Table 6. 3)

The subjective effects scale yielded three main factors, 'Perceptual disturbances' (altered time perception, altered reality, visual distortions, distortion of sound and out of body experiences), 'Somatic symptoms' (dizziness, nausea /sickness, bodily numbness, unsteadiness, lack of co-ordination) and 'Cognitive effects' (impaired

memory, confusion, impaired concentration, depression). A 4 x 3 RMANOVA of the perceptual distortions factor demonstrated a significant time x drug interaction [$F(6,153) = 23.11$ $p<0.001$] and main effects of time[$F(3,153) = 83.41$ $p<0.001$] and drug [$F(1,51) = 14.96$ $p<0.001$]. Contrasts showed that these differences were due to higher scores in both drug groups than placebo during the infusion at both 10 mins [$t(51) = 3.17$ $p<0.05$] and 80 mins [$t(51) = 7.85$ $p<0.001$] and higher scores in the high dose than low dose group 80 mins into the infusion [$t(51) = 3.51$ $p<0.001$]. RMANOVA of the somatic symptoms factor yielded a significant time x drug interaction [$F(6,153) = 17.48$, $p<0.001$] and significant main effects of time [$F(3, 153) = 89.35$ $p<0.001$] and drug [$F(1,51) = 15.25$, $p<0.001$].

Contrasts demonstrated higher scores in both drug groups than the placebo group both 10 minutes [$t(51)=4.81$ $p<0.001$] and 80 minutes[$t(51)=8.08$ $p<0.001$] into the infusion. Analysis of the subjective 'Cognitive effects' again demonstrated a significant interaction time x drug [$F(6,153) = 18.90$ $p<0.001$], main effects of time [$F(3,153)=112.65$ $p<0.001$] and drug [$F(1,51) = 11.97$ $p<0.001$]. After calculating contrasts it was found that both drug groups had higher scores than the placebo group 10 minutes [$t(51)=3.58$ $p<0.01$] and 80 minutes [$t(51) = 8.69$ $p<0.001$] into the infusion and that the high dose ketamine group had significantly higher scores after 80 minutes of infusion [$t(51) = 2.78$ $p<0.01$].

6.4.4 Correlations

Given the suggestions that an interaction between the drug's reinforcing effects and response inhibition may underlie the formation and maintenance of drug abuse, the relationship between these two variables was examined. In order to minimise the number of correlations conducted, correlations were only conducted between the Hayling errors of response inhibition and the 'like effects of the drug' and 'want more of the drug' visual analogue scales 80 mins post infusion. One significant correlation was found between the 'want more of the drug' visual analogue scale for the high and low dose ketamine groups and the Hayling response inhibition errors [$r = -0.37$

	Placebo				0.4 mg kg –1 ketamine				0.8 mg kg –1 ketamine			
	Pre	10 mins	80 mins	Follow -up	Pre	10 mins	80 mins	Follow-up	Pre	10 mins	80 mins	Follow-up
Drowsiness	28.48	31.29	37.04	23.20	35.13	53.54	62.49	25.62	30.10	59.25	71.95	25.96
	(16.21)	(18.68)	(20.43)	(19.54)	(13.59)	(16.20)	(13.90)	(17.61)	(15.85)	(13.95)	(15.64)	(14.65)
Anxiety	26.33	23.00	23.94	20.92	30.64	26.25	19.17	27.67	31.03	26.56	31.22	18.50
	(16.59)	(16.25)	(17.78)	(16.26)	(13.92)	(14.23)	(15.44)	(15.91)	(13.19)	(13.79)	(21.28)	(13.33)
Dis-	23.8	23.32	26.83	22.34	29.56	26.22	27.20	25.57	25.54	29.12	38.36	20.86
contentedness	(14.32)	(15.80)	(18.02)	(16.33)	(12.24)	(13.33)	(14.11)	(14.64)	(14.65)	(14.70)	(15.68)	(11.53)
Perceptual	4.52	5.17	5.70	1.26	2.06	9.17	25.04	0.83	1.30 (2.88)	17.86	49.06	0.93
symptoms	(8.57)	(5.80)	(8.76)	(2.03)	(3.06)	(8.23)	(18.04)	(1.68)		(17.60)	(22.73)	(1.35)
Cognitive	4.96	6.07	11.15	1.97	5.78	11.93	30.62	1.52	3.25 (4.12)	19.03	47.72	2.36
symptoms	(7.74)	(7.20)	(12.98)	(3.15)	(6.86)	(9.72)	(16.68)	(2.37)		(13.99)	(19.81)	(3.26)
Somatic	4.87	8.43	7.9	1.17	2.98	20.78	38.5	1.02	2.50 (3.52)	33.49	55.5	3.61
symptoms	(10.27)	(9.82)	(8.81)	(1.17)	(3.77)	(15.91)	(24.74)	(1.88)		(21.17)	(27.65)	(7.26)

Table 6.3: Mean (s.d) scores on the three factors of the mood rating scale, and bodily symptoms scale across treatment condition and assessment point

p=0.025]. There was a trend towards a correlation between the 'like more of the drug' and the Hayling response inhbition errors [r=-0.32 p=0.057]. There were no correlations between SSQ and ADDS scores and the Hayling test.

6.5 Discussion

There are two main novel findings of the present study. Firstly, an acute dose of ketamine decreased response inhibition and was subjectively reinforcing in healthy volunteers. Secondly, there were no residual cognitive impairments or schizotypal/ dissociative effects three days after drug administration. This study also replicated previous findings in that ketamine acutely impaired prose recall and increased schizophrenia-like and dissociative symptoms (e.g. Krystal et al., 1994; Malhotra et al., 1996; Harborne et al., 1996; Newcomer et al., 1999; Adler et al., 1998; Hetem et al., 2000).

Response inhibition was found to be impaired in this study. As far as we are aware, this is the first study to directly examine the effect of ketamine on response inhibition in humans. Ketamine-induced impairments in response inhibition have been found previously on tasks such as the WCST (Krystal et al., 2000) that involve inhibitory processes but that also tap more complex mechanisms including procedural learning and working memory. It is important to note that no one task taps a single cognitive process, and hence the response inhibition deficits observed here may be related to working memory impairments induced by ketamine (e.g. Krystal et al., 1994; Chapter 2). However as there were no group differences in responses on part I of this task, which placed a similar load on working memory as part II of the task, then deficits on part II may reflect a selective inhibition deficit.

This study is also the first to examine the reinforcing aspects of ketamine administration in humans. Subjective ratings of 'high' induced by ketamine have been previously examined (Krystal et al., 1994; Krystal et al., 1997), however these

measures give no indication of the degree to which the drug is reinforcing. Ratings of desire for the drug and the degree to which drug effects were pleasant were increased in both drug groups but most highly in the low dose ketamine group. So even in non-drug abusing healthy humans, ketamine has dose dependent reinforcing effects. The high dose group, on the other hand, felt the effects of the drug most strongly as one would anticipate.

The findings of this study are consistent with the pre-clinical literature which suggests that NMDA antagonists disrupt response inhibition on tasks such as the 5-choice serial reaction time task where premature responding has been observed (e.g. Higgins et al., 2003) and where ketamine has been found to be self-administered (e.g. Marquis et al., 1989). These results also relate to the abuse literature where impaired response inhibition and salience attribution have been proposed to underlie drug addiction (I-RISA - Golstein & Volkow, 2002). Salience attribution refers to both the experience of strong positive reinforcement and attribution of primary salience to the drug. Whilst the subjective measures used in this study do not directly assess salience attribution, they reflect to some degree the extent to which the drug has become a reinforcing, positive stimulus ('Like the drug...') and the extent to which this reinforcement is salient ('Want more of the drug...). Hence, the low correlation that was observed between the response inhibition measure and the participant's subjective rating of their desire for more of the drug in this study may relate to the I-RISA model. This relationship suggests that these two processes may form part of a common circuit in drug abuse.

Ketamine's effects on dopamine (DA) may have contributed to these findings, as DA modulation is common to drugs of abuse. Ketamine is known to have dopaminergic effects both directly through its low affinity action at dopamine reuptake sites and indirectly through NMDA-receptor modulation of dopaminergic systems (Irufine et al., 1991; Javitt & Zukin, 1991; Smith et al., 1998). However, in animals, the effect of ketamine on dopamine is not correlated with its NMDA-antagonist-like discriminative properties (Snell et al., 1984). Also, the subjective 'high' induced by ketamine is also not affected by pre-treatment with a dopamine antagonist in humans (Krystal et al.,

1997). The animal literature suggests that ketamine-mediated dopamine effects increase DA release in the prefrontal cortex (PFC) at low doses (Verma & Moghaddam, 1997) but interfere with the action of DA uptake sites at higher doses (Smith et al., 1981). The above differing mechanisms might potentially explain the biphasic drug effects observed in the current study as the lower dose being more reinforcing at 80 minutes than the higher dose. Recent preclinical evidence suggests that alterations in glutamatergic transmission are related to aspects of compulsive drug use, thus it is possible that ketamine-induced changes in glutamatergic transmission may also be responsible for the response inhibition deficits and associated drug incentive salience observed in this study. As other drugs, such as ethanol, with NMDA-receptor and glutamatergic action acutely disrupt response inhibition (Finn et al., 1999), a common mechanism may be involved in these deficits. In a previous study of recently detoxified alcoholics, ketamine failed to induce alcohol craving, however it did produce subjective ethanol-like effects (Krystal et al., 1998c). These ethanol-like effects were anecdotally noted by participants in the present study, particularly in the low dose group, many of whom likened the experience to being 'quite drunk'. It is possible that this may have contributed to the low dose group's desire for more of the drug and strong enjoyment of its effects. The high dose group reported stronger psychotomimetic effects, and thus the experience was less ethanol-like which may explain differing responses between the high and low dose ketamine groups on these scales. The above mechanisms may underlie the continued abuse of ketamine. Ketamine dependence has been reported anecdotally (Grinspoon & Bakalar, 1997; Siegel, 1978; Ahmed & Petchovsky, 1980; Hurt & Ritchie, 1994; Jansen, 1990; Kamaya & Krishna, 1987a), and is thought to be an increasing problem amongst abusers of this drug (Jansen, 2001). Further understanding of the relationship between this apparent disruption in inhibitory processes and increased drug incentive salience may benefit both models of drug addiction and understanding of the mechanisms of compulsive ketamine use.

The second major finding of this study was that there were no residual effects following an acute dose of ketamine in healthy volunteers on measures that demonstrated impairments in ketamine abusers. This extends the findings of Newcomer et al. (1999)

who found no residual schizophrenic symptoms 48 hours after a ketamine infusion. The lack of residual cognitive effects observed in this study is interesting in light of research with recreational users where residual impairments on these cognitive tasks were found (Curran & Morgan, 2000; Curran & Monaghan, 2001). This would seem to indicate that residual effects in recreational users are not related to transient brain changes, as a result perhaps of residual levels of the metabolite norketamine, but indicative of chronic effects or pre-existing differences in abusers and non-abusers. If the impairments in recreational users are chronic effects, then they may possibly relate to lasting neurotoxicity, similar to that observed in animals (Olney et al., 1991). Pre-existing differences are difficult to rule out without prospective studies but the suggestion of chronic effects following repeated ketamine use has serious implications for the growing population of abusers. Chronic ketamine effects are also relevant to prescribing practice in some areas of medicine, such as chronic pain, where repeated doses of ketamine are often used (Hewitt, 2000). This lack of residual effects also offers ethical reassurance for future acute ketamine studies, in that prolonged effects following a single dose are not apparent, contrary to those observed in the PCP literature (Ellison, 1995).

Acutely ketamine also impaired prose recall, replicating the findings of previous studies (e.g.Harborne et al. 1996) and further establishing the role of the NMDA-receptor in episodic memory. Ketamine impaired memory for information learnt under the influence of the drug but not for information learnt prior to drug administration, hence supporting prior evidence suggesting ketamine's effects on memory are as a result of encoding and not retrieval deficits (Malhotra et al., 1996; Hetem et al., 2000). Fluency, which taps frontal functioning was not affected by ketamine administration. This replicates the findings of some previous ketamine studies (Newcomer et al., 1999; Krystal et al., 2000; Abel et al., 2003) and yet differs from others (Adler et al., 1998; Krystal et al., 1994). It also differs from findings in populations of recreational users where category fluency has been found to be impaired with more errors made both acutely and residually (Curran & Morgan, 2000; Curran & Monaghan, 2001). The preserved fluency observed in the current study also indicates a selective sparing of

some frontal functions, which suggests that response inhibition deficits were not as a result of a global impairment in executive functioning. Neuroimaging studies have found verbal fluency to be associated with activity in the left dorsolateral prefrontal cortex (Frith et al., 1991) whereas the orbitofrontal cortex and anterior cingulate have been implicated in response inhibition (Casey et al., 1997; Goldstein et al., 2001). Acute ketamine administration is associated with hyperfrontality and decreased activation in the anterior cingulate (Breier et al., 1997; Lahti et al., 1995a; Vollenweider et al., 1997). The behavioural data of the current study may indicate selective hyperactivation in some frontal regions. Ketamine acutely increased schizophrenic-like and dissociative symptoms, again replicating previous studies (e.g. Krystal et al., 1994). Visual analogue scales of mood and subjective effects reflected changes consistent with reports in the ketamine literature, such as increases in drowsiness and alterations in perceptual experiences. The subjective effects of perceived cognitive and perceptual disruptions were related to the dose of ketamine given, whereas somatic symptoms were not dose-dependent, and may be related to individual differences.

In summary, this study has replicated data from previous studies suggesting an episodic memory impairment, preservation of fluency and increase in schizotypal and dissociative symptoms. In addition, this study demonstrated no residual cognitive effects three days following administration of an acute dose, on measures that demonstrated residual effects in recreational users. Finally, related to recent preclinical findings (Higgins et al., 2003), an impairment in response inhibition was observed acutely following ketamine and was found to be related to increases in subjective ratings of desire for the drug. Further work is necessary to fully explore these mechanisms as this may elucidate the role of response inhibition and salience attribution in drug, and particularly, ketamine abuse.

Chapter 7: Just say 'No-go' to drugs

Response inhibition following acute ketamine in healthy volunteers and response inhibition and salience attribution in recreational ketamine users

"Frequent use of ketamine can lure one as an escape since a blissful and fantastic state of fearless, disembodied consciousness is so easily available..."
D.M.Turner (1994) The Essential Psychedelic Guide

7.1 Overview

In theories of drug abuse and dependence, two processes have been emphasised. The first is an alteration in motivation whereby drug stimuli become more salient than other 'natural' reinforcers. The second is reduced 'impulse control' or inhibitory processes. The study reported in this chapter had three main aims: 1) to further investigate whether acute ketamine impairs response inhibition in healthy volunteers 2) to investigate whether response inhibition is impaired in ketamine users and poly-drug users compared to non-drug using controls 3) to investigate whether ketamine users find ketamine stimuli more salient than 'natural' reinforcers. We examined the effects of two doses of ketamine on response inhibition using a Go/No-go task in healthy volunteers with a double-blind, placebo-controlled independent groups design (Experiment 1). We tested ketamine users, poly-drug controls and non-drug users were tested on the same Go/No-go task and additionally on a novel 'Drug Go/No-go task' (Experiment 2). The latter paradigm aimed to investigate salience attribution and response inhibition within the same task. In Experiment 1, acute ketamine reduced the number of hits on the Go/No-go task. In Experiment 2, on the night of drug use ketamine both increased false alarms and decreased hits on the Go/No-go task. When drug free, there were no differences in response inhibition between the three groups.

There was some evidence on the Drug Go/No-go that drug users, i.e. poly-drug controls and ketamine users, had reduced attentional bias to 'natural' incentive stimuli. The indication of reduced attentional bias to 'natural' incentive stimuli in recreational drug users is interesting and should be further investigated, however problems with the novel Drug Go/No-go task complicated interpretation of these data.

7.2 Introduction

Ketamine dependence, as discussed in Chapter 1, has been reported in the popular press (Lilly, 1978; Sputz, 1989; Turner, 1994) and there have been a number of similar case reports in the medical literature (Ahmed & Petchovsky, 1980; Hurt & Ritchie, 1994b; Jansen, 1990; Lim, 2003; Moore & Bostwick, 1999; Pal et al., 2002; Soyka et al., 1993; Kamaya & Krishna, 1987b). In rats and non-human primates, ketamine is repeatedly self-administered (Marquis et al., 1989; Winger et al., 1989). Ketamine also produces conditioned place-preference in rats (Layer et al., 1993). An acute dose of this drug also increases ratings of subjective 'high' in healthy humans (Krystal et al., 1998b; Krystal et al., 1994). Further, healthy volunteers rated themselves as liking the effects of ketamine and wanting more of the drug after a single dose (Chapter 6; Morgan et al., 2004b). It seems intriguing that these 'schizophrenia-like' effects can be perceived as pleasant and desirable even by non-drug users.

The desire to take a drug again and the degree to which its effects are perceived as pleasurable are thought to be governed by a complex interplay of several factors. Whilst more recently other neurotransmitter (NT) systems have been suggested to be involved (e.g. glutamatergic, Cornish et al., 1999) traditionally, the mesolimbic dopamine circuit is considered crucial in mediating the rewarding properties of drugs of abuse (Koob, 1992). Repeated stimulation of dopamine circuits is thought to lead to abnormal reward dependent learning (Di Chiara, 1999). Thus the drug user learns to strongly associate the drug of choice and cues connected to it, including people and places, with pleasure and reward.

It is thought that in drug users, this abnormal reward dependent learning leads to primary salience being attributed to the drug (Robinson & Berridge, 1993), at the expense of other available rewarding stimuli in the environment (Goldstein and Volkow, 2002). An example of how this is manifested in drug users' lives is the version of the 'cocktail party phenomenom' (Moray, 1959) experienced by heavy drug users.

Drug dependent individuals report that, even in a noisy environment, conversations that mention drugs capture their attention suddenly. The attention- grabbing properties of drug stimuli have been shown in a variety of drug using populations, for example in heroin addicts as a bias to drug- salient pictures in dot-probe tasks (Lubman et al., 2000) and in alcohol dependent individuals with the Stroop task (Stetter et al., 1995). Wanting drugs over other available rewards in the environment is apparent from the manner in which drug users, and in particular drug dependent individuals, will rather take drugs than engage in more 'naturally' rewarding activities such as eating. Related to this, response to monetary rewards has been found to be reduced in abstinent smokers and restored after one cigarette (al-Adawi & Powell, 1997). However, as far as we are aware, no studies in the drug abuse field have addressed the issue of salience of drugs in direct comparison to other non-drug incentive stimuli.

Salience attribution is thought to be reliant on the frontal cortex interacting with limbic regions to determine the value of a reward and is particularly reliant on dopaminergic (Dayan & Balleine, 2002) and to a lesser extent glutamatergic (Reynolds & Berridge, 2003) transmission. As ketamine stimulates both dopamine and glutamate release (Moghaddam et al., 1997), defective salience attribution processes may contribute to the maintenance of ketamine abuse.

Despite the clear role of 'wanting' and 'liking' the drug, users will continue to use a drug even when it ceases to be rewarding (Fischman et al., 1985), hence it has been postulated that the rewarding effects of drugs are necessary but not sufficient for the development of drug abuse (Goldstein & Volkow, 2002). Impairments in the cognitive domain are also thought to be key to the maintenance of substance misuse.

Frontal functioning is thought to be particularly impaired in drug users. It has been suggested that in compulsive drug use, prefrontal top-down processes are compromised and inhibitory control is reduced, leading to accentuated stimulus-driven behaviour. Substance abuse is thought to result in part from a breakdown in the control of self-generated behaviour (Goldstein & Volkow, 2002). This renders users less able to

prevent themselves seeking and then taking the drug. Research has found deficits in response inhibition in various drug using populations (Powell et al., 2002; Fillmore & Rush, 2002a) which supports this assertion. An acute dose of ketamine may also impair response inhibition in healthy volunteers (Chapter 6; Morgan et al., 2004d). It is therefore plausible that a breakdown in response inhibition could go some way to explaining the desire to repeatedly use ketamine. In support of this, frontal functioning as indexed by perseverative errors on a verbal fluency task was found to be impaired in frequent compared to infrequent ketamine users both on drug and when drug free (Curran & Monaghan, 2001). No research has addressed whether, amongst other frontal functions, response inhibition specifically is impaired in ketamine users.

These concepts of deficits that contribute to drug abuse have been brought together in the 'Impaired Response Inhibition and Salience Attribution' (I-RISA) model (Goldstein & Volkow, 2002). Whilst, it is accepted that many other processes are involved in deciding both the rewarding properties and maintenance of drug abuse (e.g. motivational, learning, affective) the latter authors propose that compulsive drug use is a result of "...overvaluing of drug reinforcers, undervaluing of alternative reinforcers and deficits in inhibitory control for drug responses..." (Goldstein & Volkow, 2002 pp. 1642).

Given that impaired salience attribution and response inhibition are suggested in drug abuse, it seemed reasonable to speculate that ketamine users may show abnormal salience attribution to ketamine related-stimuli compared to other non-drug incentive stimuli. Specifically, ketamine users may also show particularly poor response inhibition to ketamine-related stimuli. We therefore developed a task to examine responses to drug related stimuli, compared to non-drug incentive stimuli (i.e. food, sex and money) and neutral stimuli (e.g. furniture). Importantly, we also designed the task to concurrently examine the ability to inhibit responses to these three different stimuli, thereby testing both components of the I-RISA model within the same task. This 'drug Go/No-go task' described below was employed in our fourth study of ketamine users.

The aims of this study were three-fold. Firstly, we wished to investigate response inhibition following acute, acute on 'chronic' and 'chronic' ketamine. This was done in three ways, i) using a conventional Go/No-go task, in healthy volunteers following an acute dose of ketamine (Experiment 1) ii) using the same Go/No-go task in ketamine users both on the night of drug use (day 0) and then three days later (day 3) when drug free (Experiment 2) ii) using the novel Drug Go/No-go task on the 3rd day after drug use (Experiment 2). For the drug user studies, three groups of participants were compared: ketamine users, poly-drug controls and non-drug users. Drug using controls were used as an additional comparison group because ketamine users are a population of poly-drug users and thus to isolate the effects of ketamine it was important to compare not only to non-drug users, but to a group matched for drug use apart from ketamine. Based our previous findings of response inhibition impairments following an acute dose of ketamine in healthy volunteers on a complex response inhibition task (Morgan, 2004b; chapter 6) we predicted that acute ketamine would produce response inhibition impairments in Experiment 1. In Experiment 2 we predicted that, on day 0, ketamine users would demonstrate poorer response inhibition than poly-drug controls and non-drug users. Additionally we speculated that poly-drug users may also show reduced response inhibition compared to non-drug controls based on findings of greater impulsivity in poly-drug users (M.Morgan, 1998). On day 3, we predicted that response inhibition deficits would be reduced in ketamine users relative to day 0 but that both ketamine and poly-drug users would have impaired response inhibition compared to non-drug users (M. Morgan, 1998). We also tested response inhibition, by examining overall errors on the novel 'Drug Go/No-go' task.

The second aim was to examine salience attribution in drug users. We hypothesised that ketamine users should show an attentional bias towards ketamine-related stimuli. As our control groups both used alcohol and one used cannabis, we speculated that they may show more bias towards alcohol and cannabis than ketamine stimuli. We predicted that all participants would show a bias to incentive stimuli (food, sex, money related) compared to neutral, but based on the I-RISA model that the bias may be smaller in drug users compared to non-drug users. Our novel task was designed so that we could

also test response inhibition to different types of stimuli in the same three groups of participants. We hypothesised that non-drug users would exhibit most false alarms and quickest reaction times to non-drug incentive stimuli, whereas the ketamine users should show most false alarms and quickest RTs to ketamine-related stimuli. We also aimed to use this study to pilot the novel Drug Go/No-go task to examine its feasibility and sensitivity to drug effects in a population of recreational drug users.

Experiment 1 – Response inhibition following and acute dose of ketamine

7.3 Method

7.3.1 Design, Procedure, Particpants

These exactly followed those reported in Chapter 3. Thus 48 participants were randomly allocated to receive either ketamine (low-dose or high-dose) or placebo (0.9% NaCl solution). As part of the test battery administered, we also examined performance on the Go/No-go task before drug administration and during the infusion.

7.3.2 Go/No-go task:

This task tapped response inhibition and response reversal. The task consisted of three blocks: a practice block of 40 stimuli and two blocks of 100 stimuli (the task is depicted in Figure 7.1). Stimuli were 16 characters of the alphabet organised into two sets of 8. For the practice block participants were instructed to respond, by pressing a designated key on the computer keyboard as quickly as possible, to each letter on the screen. Each letter appeared for 800ms followed by an inter-stimulus interval (ISI) of 500ms. In the first test block (Phase 1) participants were instructed to respond by the same designated key press to all but two (e.g. L, C) of the eight letters. These two letters constituted the 'Nogo' trials. The proportion of 'Go' stimuli was 75% and of 'No-go' stimuli was 25%. Participants were then given a short break and then were presented with the second test block (Phase 2) and were then instructed not to respond to a different two (e.g. Q, N) of the eight letters . This required participants to respond to the two letters for which responses were required to be inhibited in the previous block (e.g. L, C), thus tapping response reversal. Scores were recorded in terms of false alarms (commission /

response inhibition errors), hits (correct responses), misses on reversal trials and reaction times.

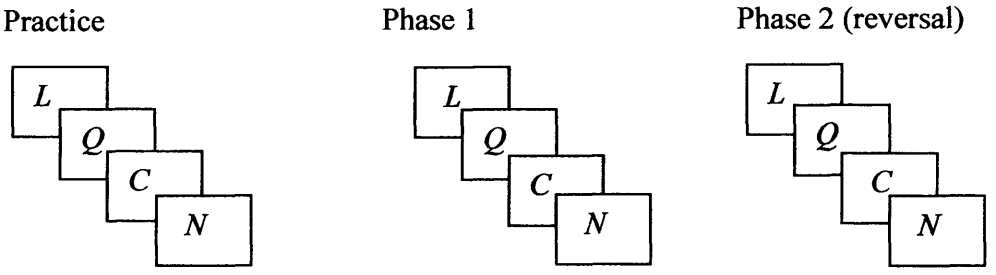


Figure 7.1: Schematic of the Go/No-go task

Subjective Ratings: the SSQ, ADDS, MRS were administered and results are reported in Chapter 3.

7.3.3 Statistical Analysis

Go/No-go data from day 0 were analysed using a repeated measures analysis of variance (RMANOVA) with Time (Pre-drug, Post drug) and Phase (1 - response inhibition or 2 - response inhibition & reversal) as the within subjects factors and Group (high dose ketamine, low dose ketamine or placebo) as the between subjects factor. Scheffe's test was used to analyse significant interactions on the Go/No-go with the alpha level adjusted to 0.0167 to control for multiple comparisons. Non-significant main effects and interactions are not reported.

7.4 Results

7.4.1 Go/No-go task

Analysis of the correct responses on the Go/No-go demonstrated a significant main effect of Time [$F(1,45) = 20.83$, $p<0.001$] and a Group by Time interaction [$F(2,45) = 3.39$, $p=0.044$]. Post-hoc tests demonstrated significantly lower hits post drug in the high dose group compared to the placebo ($p =0.043$) and low dose ($p=0.026$) – See Figure 7.2.

For the false alarm data, there was a significant main effect of time [$F(1,45) = 6.29$, $p=0.016$] whereby more false alarms were made during the infusion than before.
There were no differences in the number of reversal omission errors pre and post drug in any of the groups.

For reaction times to hits, there was a main effect of Phase [$F(1,45) =48.84$, $p<0.001$] and a significant Phase x Time interaction [$F(1,45) = 6.80$, $p=0.013$]. There was a significant decrease in reaction time for Phase 1 pre and post drug ($p<0.001$) but no difference in reaction time pre and post drug for Phase 2.

Reaction time to FAs, for those subjects that made false alarms on all sections of the task, yielded a similar main effect of Time [$F(1,34) = 15.86$, $p<0.001$] and a Phase x Time interaction [$F(1,34) = 5.51$, $p=0.025$]. There was a significant decrease in reaction time to false alarms on Phase 1 pre to post drug ($p<0.012$).

Mean hit, false alarm and reaction time data are presented in, the Appendix Table A3.

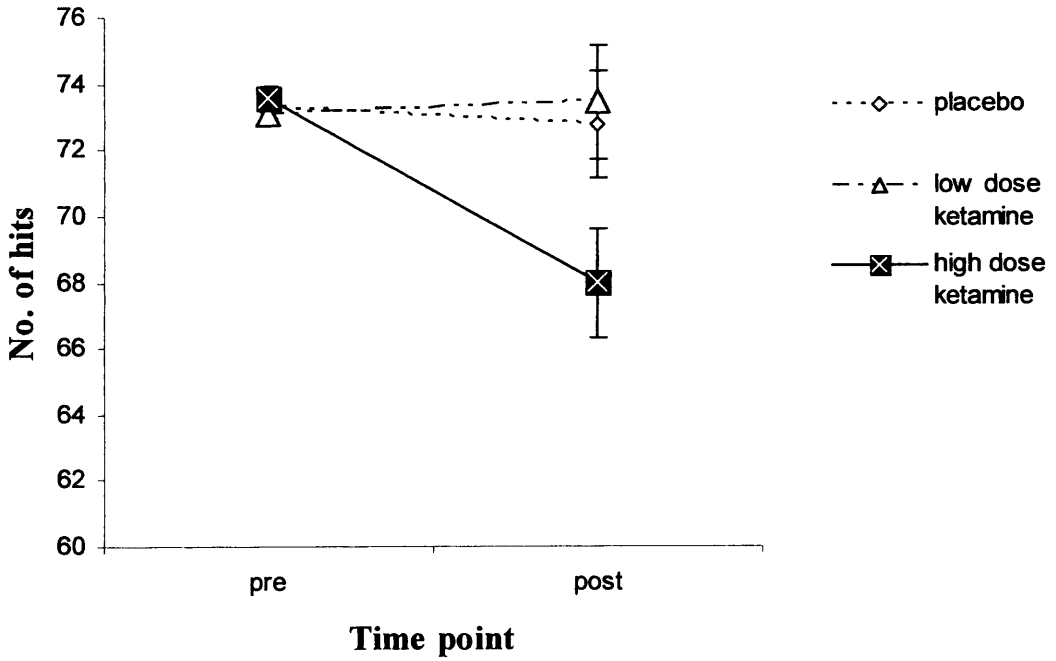


Figure 7.2 : Number of hits on the Go/No-go task pre and post drug across treatment condition.

7.4.2 Subjective Effects : These are reported in Chapter 4.

Experiment 2 : Response inhibition and salience attribution in recreational ketamine users

7.6 Method

7.6.1 Participants and Design

Participants were recruited at dance music venues using a snowball sampling technique (Solowij et al., 1992). They were tested on two occasions: on day 0, when the ketamine group were under the influence of the drug and again 3 days later. Test versions were counterbalanced across group and day. The study was approved by the institutional ethics committee and was conducted in accordance with the Declaration of Helsinki.

7.6.2 Procedure

Participants were approached in a party setting on day 0 by the experimenters and asked if they were interested in taking part in a study about drug users. If they agreed volunteers were taken individually to a quiet area where they were given full information about the study and informed the experimenter what, if any, drugs they had taken or intended to take that evening. They were excluded if they had taken any drugs other than 1) ketamine or 2) small amounts of cannabis (< 1 "joint") or more than 2 units of alcohol that evening. Participants on ketamine were asked to estimate when they had taken the drug, and only participants who had recently taken ketamine (i.e. within 10 minutes) were included. Participants then completed the assessments detailed below and arrangements were made to meet up 3 days later. The task battery lasted approximately 30 minutes. Participants were asked to abstain from using alcohol and other recreational drugs between the two test sessions. The follow-up test session on day 3 was carried out in the participant's home or in a recreational centre, in a room with minimal distraction. They then completed the same assessments as on day 0 along with a pre-morbid IQ measure and a detailed drug-use questionnaire. Participants provided written, informed consent on both days of testing.

7.6.3 Assessments

Go/No-go : Details of this task are given above in Experiment 1. Participants were tested on Day 0 and Day 3.

Drug Go/No-go: Day 3

This novel task is designed to tap response inhibition and salience attribution. Stimuli were 54 words, 6 each from 3 separate categories: drug related words (ketamine, cannabis or alcohol-related), incentive words (food, sex and money related) and neutral words (furniture, fabric and building-related) (See Fig 7.3). Non-drug words were chosen from the MRC psycholinguistic database (http://www.psy.uwa.edu.au/MRCDataBase/uwamrc.htm) and matched between categories for imageability. Words were selected from an original list of 135 (approx.

15 per group). Drug words were rated by 5 ketamine users, 5 cannabis users and 5 alcohol users (not included in this study and blind to its purpose) for representativeness of category and valence.

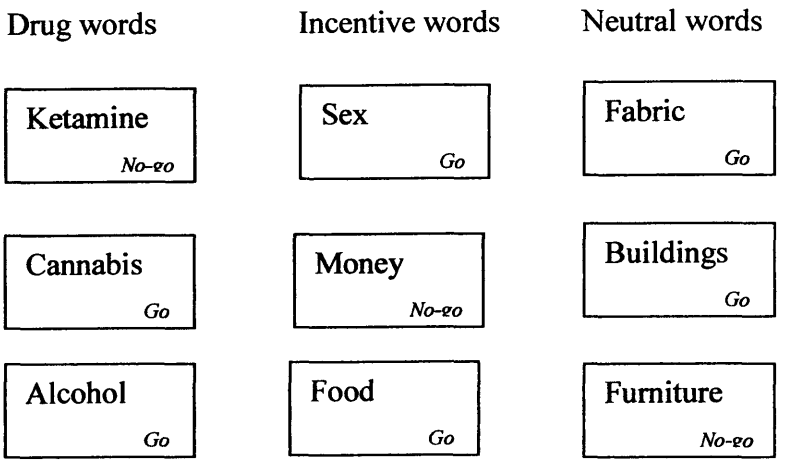


Figure 7.3: The 'Drug' Go/no-go task.

The final words (See Appendix Table 4A) were selected on the basis of these ratings, i.e. the most representative of the category and the most positive valence. As 6 unambiguous words could not be generated for the ketamine category, all groups of drug words contained three ambiguous and 3 non-ambiguous drug words. All stimuli were matched for word length, number of syllables and within category for frequency and ambiguity. Stimuli were presented in 9 blocks of 18, each block containing one set of words from each category. Each block contained 3 different sets of words to the block before, and words were pseudo-randomly presented within each block. Stimuli were presented in the centre of computer screen using DMDX software for 1000 msec with a 100 msec inter-stimulus interval (I.S.I). In each block participants were instructed not to respond to a particular category of words (e.g. ketamine-related words) but to respond to all other words (e.g. sex and fabric related words). Before the task participants were given a list containing all the words in each category to familiarise themselves with for 2 min. Then they were given a practice block containing different types of stimuli (all neutral) from those included in the task before moving on to the task itself. Performance measures were hits (number of targets correctly responded to),

false alarms (number of commission errors) and reaction times. The task provided 3 measures: i) overall performance irrespective of the nature of stimuli as a general measure of inhibitory control (false alarms); ii) an index of comparative salience of the different types of stimuli (e.g. incentive vs. drug - indexed by speed of response to the different stimuli); iii) a measure of response inhibition and salience attribution indexed by the number of false alarms to different types of stimuli.

Spot the word test (Baddeley et al., 1993): Participants were required to choose the real word out of pairs of words/non-words. This task has been shown to give a measure of IQ that is correlated 0.69 with the National Adult Reading Test (NART: (Crawford et al., 2001).

Subjective Ratings

Ratings used in previous studies (SSQ, ADDS, MRS, SES) were again employed on both day 0 and day 3. Two additional scales were administered on day 3:

Peter's Delusions Inventory (Peters et al., 1999)

A 30-item questionnaire tapping delusional beliefs, in which participants also rated whether they held certain delusions with a yes/no response and then rated their distress, preoccupation and conviction regarding the delusion on a five point scale.

Barratt Impulsivity Scale (Patton et al., 1995)

A 30-ietm questionnaire was used to examine trait impulsivity. The scale has 3 factors: Attentional Impulsiveness, Motor Impulsiveness, and Nonplanning Impulsiveness.

7.6.4 Urine analysis

Participants were asked to give a urine sample to test for drug use (cannabis, MDMA, amphetamines cocaine, opiates, ketamine and benzodiazepines) on day 0 and day 3.

7.6.5 Statistical Analyses

Go/No-go data from day 0 and day 3 were analysed using a repeated measures analysis of variance (RMANOVA) with Day (0 or 3) and Phase (1 - response inhibition or 2 - response inhibition & reversal) as the within subjects factor and Group (ketamine, poly-drug or non-drug) as the between subjects factor. Scheffe's test was used to analyse significant interactions on the Go/No-go with the alpha level adjusted to control for multiple comparisons.

Drug Go/No-go data was also analysed with a RMANOVA with Stimulus type (drug, incentive or neutral) as the within subjects factor and Group as the between subjects factor as above. Where significant interactions were obtained 2 planned orthogonal contrasts were conducted: I) ketamine vs poly-drug and non-drug controls II) drug users vs. non-drug users. If there were significant differences for the 'drug' stimuli a further RMANOVA was conducted with Drug stimulus type (ketamine, cannabis, alcohol) and the within subjects factor and Group (ketamine, poly-drug, non-drug) as the between subjects factor. The above contrasts were again conducted where significant interactions were found. There were no differences in responses to the different sets of words within the categories 'neutral' and 'incentive' so data were collapsed across the sets.

Subjective ratings on day 0 and 3 were also analysed with a RMANOVA (day, group). For demographic, trait questionnaire and drug use data one-way ANOVAs were conducted if the data were parametric and Kruskall-Wallis or Mann-Whitney U tests for non-parametric data dependent on the number of groups.

7.7 Results

7.7.1 Demographics and drug use

58 participants initially took part in the study, 5 dropped out before follow-up and 3 were excluded (1 non-drug participant tested positive for cannabis and 2 of the ketamine group reported drug use between day 0 and day 3). 50 participants completed

the study; 20 ketamine users (mean age 22.55 ± 1.18 years, 8 females), 17 polydrug using controls (mean age 22.00 ± 1.70 years, 6 females) and 13 non-drug using controls (mean age 22.00 ± 0.01 years, 3 females). There were no significant differences in age, sex or premorbid IQ [Spot the word test score - ketamine: 48.10 ± 4.78; poly drug control: 50.24 ± 2.86; non-drug control: 46.3 ± 3.95]. The non-drug group did not report the current use of any recreational drugs except alcohol, where they were matched with the other groups [mean alcohol use non-drug – 14.3 (6.43) days per month; 7.51 (2.45) units per session; for 6.35 (2.56) years]. Six participants in the non-drug group reported trying cannabis on a maximum of 3 occasions, but all had been abstinent for over a year. The ketamine and poly-drug control groups did not differ in lifetime prevalence of drug use (see Table 7.1) but differed in years of regular MDMA use ($U= 90.50$, $p<0.014$). Ketamine users had used ketamine for a mean of 2.70 ± 0.36 days per month, using 0.46 ± 0.10 grams per session and had taken the drug for 2.19 ± 0.40 years.

All ketamine users who provided a urine sample (n=17) tested positive for ketamine on day 0. On day three, one of the ketamine group tested positive for ketamine but was not excluded as they claimed not to have taken ketamine for 3 days; 16 tested positive for THC. All of the control group who were tested (n=15) tested positive for THC on both days, but no other drugs. Of the non-drug group (n=13) none tested positive for any drugs of abuse.

7.7.2 Cognitive Assessments

7.7.2.1 Drug Go/No-go

Due to a recording error data for 2 participants in the ketamine group were lost therefore for this task: ketamine group (n=18), poly-drug control (n=17), non-drug (n=13).

There were no differences in the number of hits across groups or across the different stimuli on the Drug Go/no-go task. A RMANOVA of the reaction times for hits (to

Drug, Neutral or Incentive words) yielded a significant Group x Stimulus type interaction [F (4,90) = 3.33 p=0.014]. Contrasts demonstrated faster RTs to incentive words in the non-drug group compared to the drug groups [t(45)=2.35 p=0.023] but no other differences. (Fig 7.4) Analysis of RTs to drug stimuli did not produce any significant group differences.

Drug	Days/Month		Amount/session		Years taken	
	PD control N=17	Ketamine users N=20	PD control N=17	Ketamine users N=20	Control users N=17	Ketamine users N=20
Alcohol	17.53 (7.24)	17.85 (7.19)	9.12 (3.77)	9.00 (3.28)	6.18 (1.85)	6.65 (3.05)
Cannabis	10.12 (9.49)	14.40 (10.45)	2.34 (1.71)	2.53 (2.30)	6.00 (2.65)	6.03 (3.11)
Cocaine	1.06 (1.48)	1.05 (1.47)	0.45 (0.36)	0.29 (0.33)	2.82 (1.13)	2.90 (2.34)
Ecstasy	1.18 (1.38)	1.20 (0.77)	1.47 (1.12)	2.15 (0.81)	2.29 (1.65)	4.03* (1.90)
Tobacco	13.59 (14.04)	17.80 (13.82)	5.06 (6.57)	4.60 (5.19)	2.18 (2.72)	3.45 (3.32)

Alcohol (no. units); cannabis (no. joints - 1 gram calculated to be approx. 6-8 joints); ecstasy (no. tablets); tobacco (no. cigarettes) * $p<0.01$, PD = Poly-drug

Table 7.1: Means and standard deviations for drug use by experimental group and control.

	Ketamine users	Poly-drug controls	Non-drug controls
No. Hits ketamine	11.67 (0.76)	11.29(1.69)	10.69 (1.37)
No. Hits cannabis	11.02 (1.21)	11.44 (0.66)	10.78 (2.38)
No. Hits alcohol	11.17 (1.29)	11.47 (0.54)	11.69 (1.11)
No. Hits drug	33.86 (2.95)	34.20 (1.77)	33.15 (2.51)
No. Hits incentive	34.33 (4.64)	35.12 (1.17)	33.31 (4.64)
No. Hits neutral	34.06 (2.41)	35.12 (1.9)	32.77 (4.71)

$p<0.05$

Table 7.2: Data for Hits on the Drug Go/ No-go task

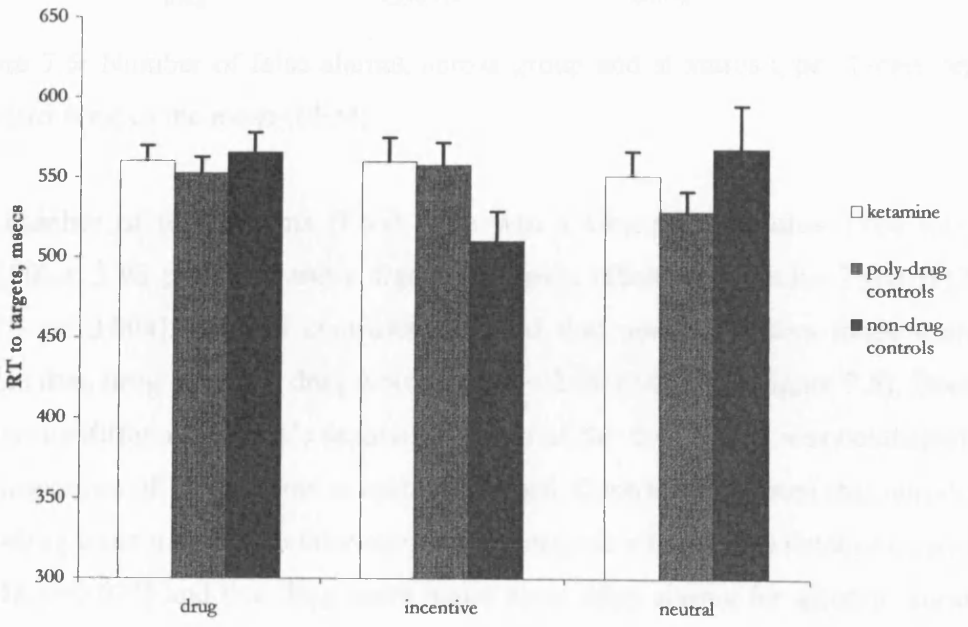


Figure 7.4: Reaction time to targets across group and stimulus type. T-bars represent SEM.

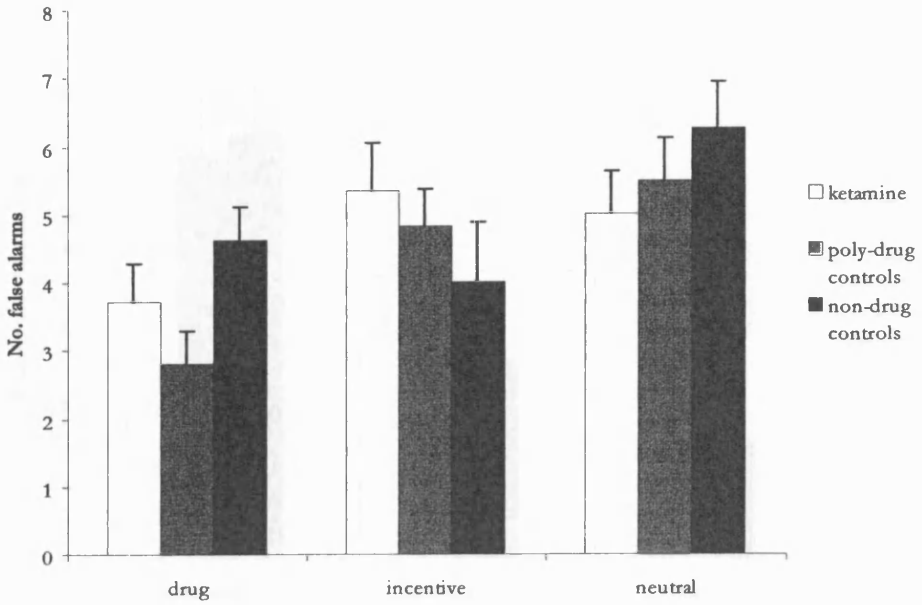


Figure 7.5: Number of false alarms, across group and stimulus type. T-bars represent standard error of the mean (SEM).

For number of false alarms (FAs) there was a Group x Stimulus Type interaction [$F(4,90) = 3.96$ $p=0.042$] and a significant main effect of Stimulus Type [$F(2,90) = 12.37$, $p= 0.004$]. Planned contrasts indicated that non drug users made more false alarms than drug users for drug words [$t(45) = 2.09$ $p=0.042$] (Figure 7.5). Because of this group difference in FA's separate analysis of the drug words was conducted, using the proportion of false alarms to each drug word. Contrasts indicated that non-drug and poly-drug users made more false alarms for ketamine stimuli than ketamine users [$t(45) = 2.18$ $p=0.035$] and that drug users make more false alarms for alcohol stimuli than non-drug users [$t(45) =2.70$ $p=0.011$] (Fig 7.6). There were no group differences in omission reversal errors.

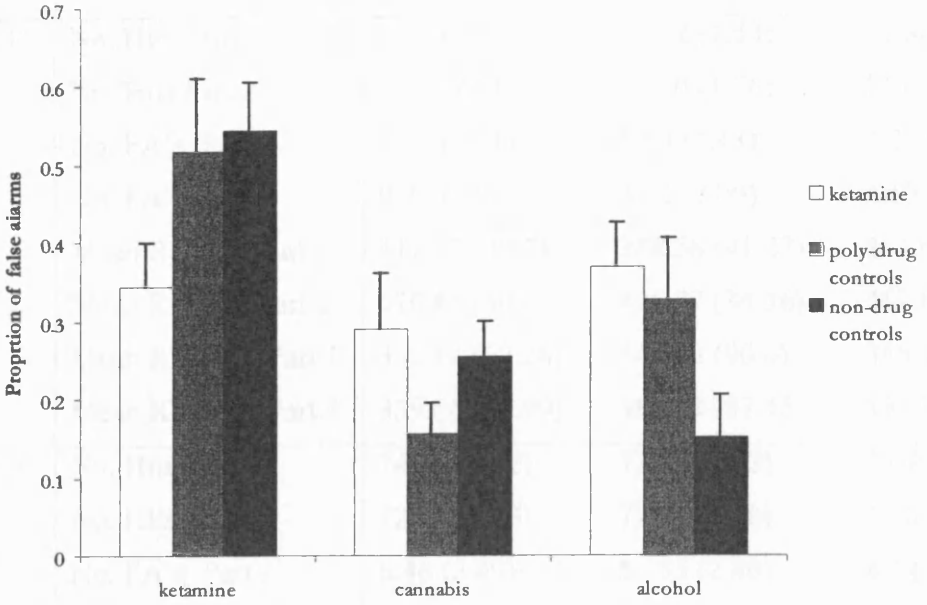


Figure 7.6: Proportion of false alarms (of total no. false alarms) for drug stimuli across group, T-bars represent SEM.

RT's for false alarms were not analysed because few participants made false alarms on all 3 types of words [control n=4, poly-drug n= 9, ketamine n=12].

7.7.2.2 Go/No-go (Table 7.3)

Analysis of hit rates on the go/no-go task demonstrated a significant Group x Day interaction [$F(2,49) = 6.77$ $p=0.03$] and significant main effects of time [$F(1,49) = 7.15$ $p=0.011$], and group [$F(2,49) = 5.55$ $p=0.008$]. A significant main effect of Phase [$F(1,49) = 18.19$ $p<0.001$] indicated all groups had fewer hits on the second (reversal) phase of the task. Exploring the Group x Day interaction with post-hoc Scheffes test, it was found that on day 0 there were significantly fewer hits in the ketamine group compared to the non-drug users and poly-drug controls at Phase 2 (both $p< 0.01$), and a trend for a difference on Phase 1 ($p<0.029$). On day 3 however, no there were no differences between the groups in either Phase.

		Ketamine users	Poly drug users	Non-drug users
Day 0	No. Hits Part 1	69.33 (7.38)	74.12 (1.83)	72.80 (2.97)
	No. Hits Part 2	65.53 (9.10)	72.70 (1.76)	71 (2.74)
	No. FA's Part 1	8.73 (3.71)	5.59 (3.43)	4.2 (3.29)
	No. FA's Part 2	9.27 (2.96)	5.82 (3.00)	4.10 (2.81)
	Mean RT Hits Part1	412.17 (35.7)	388.58 (41.27)	433.64 (78.17)
	Mean RT Hits Part 2	420.85 (30.65)	425.77 (34.56)	467.82 (68.4)
	Mean RT FA's Part 1	335.18 (57.28)	346.70 (90.0)	345.94 (47.76)
	Mean RT FA's Part 2	359.66 (53.99)	380.59 (67.45)	393.31(73.43)
Day 3	No. Hits Part 1	74.13 (1.12)	73.88 (1.53)	72.70 (1.76
	No. Hits Part 2	72.81 (2.45)	72.80 (2.40)	71.8 (1.81)
	No. FA's Part 1	6.46 (2.89)	5.255 (2.80)	4.4 (2.06)
	No. FA's Part 2	6.60 (2.92)	5.5 (2.94)	4.80 (2.97)
	Mean RT Hits Part1	392.23 (42.75)	402.28 (46.6)	422.22 (39.96)
	Mean RT Hits Part 2	422.92 (31.92)	418.43 (28.07)	457.31 (31.28)
	Mean RT FA's Part 1	339.90 (38.61)	329.87 (39.03)	362.33 (37.92)
	Mean RT FA's Part 2	394.41 (86.84)	379.26 (59.84)	450.72 (77.95)

Table 7.3: Go/No-go hits, false alarms (FA's) and respective reaction times (RTs) across ketamine users, poly-drug users and non-drug users

Reaction time data for hits showed significant main effects of Phase [$F(1,49) = 40.59$, $p<0.001$] with slower RTs for Phase 2 than Phase 1 and Group [$F(2,49) = 6.31$ $p=0.004$] Dunnett's t demonstrated significantly faster RTs in the ketamine group compared to non-drug users ($p=0.003$) but no differences between the poly-drug controls and the ketamine users. There was also a trend for a Group x Day x Phase interaction [$F(2,49) = 2.72$ $p=0.078$].

False alarm data showed a Group x Day interaction [$F(2,49) = 4.23$ $p=0.022$], a main effect of Day [$F(1,49)$ $p<0.049$] and a highly significant main effect of Group [$F(2,44) = 7.47$ $p=0.002$]. On day 0, post-hoc Scheffes tests demonstrated that false alarms rate

in the ketamine users was higher than that of the non-drug users and poly-drug controls on both versions at the $p<0.01$ level; however there were no differences between the groups on day 3.

For the false alarm reaction time data there were no group differences, but there were main effects of Day [$F(1, 44) = 16.05$ $p<0.001$], with slower RTs on day 3 for all participants and Phase [$F(1,44) = 48.76$ $p<0.001$] with slower RTs to FA's in all groups for Phase 2.

7.7.3 Subjective Effects (See Table 7.4)

7.7.3.1 Schizotypal Symptomatology Questionnaire: RMANOVA demonstrated a significant Group x Day interaction [$F(2,47) = 28.57$ $p<0.001$] and main effects of Day [$F(1,47) = 37.47$ $p<0.001$] and Group $F[2,47] = 15.79$ $p<0.001$]. Post-hoc analyses (Scheffe) showed that, there were higher levels of schizotypal symptoms in the ketamine group on day 0 than either control group ($p<0.01$) but no differences on day 3.

7.7.3.2 Adapted Dissociative Symptoms Scale: RMANOVA demonstrated a significant Group x Day interaction [$F(2,47) = 28.03$ $p<0.001$] and main effects of Day [$F(1,47) = 35.12$ $p<0.001$] and Group $F[2,47] = 39.71$ $p<0.001$]. Post-hoc analyses (Scheffe) showed that, although the level of symptoms in the ketamine group decreased between day 0 and 3, there were greater levels of dissociative symptoms in the ketamine group on both day 0 and 3 than either control group ($p<0.01$).

7.7.3.3 Mood Rating Scale: There was a significant Day x Group interaction for the mood factor of sedation [$F(2,47) = 8.056$ $p<0.007$], as well as main effects of Day [$F(1,47) = 8.056$ $p<0.001$] and Group [$F(2,47) = 5.92$ $p<0.005$]. Scores were higher in the ketamine group than the other two groups ($p<0.01$) on day 0.

		Ketamine users	Poly-drug controls	Non-drug controls
DAY 0	SSQ	30.06 (13.08)	9.75 (2.07) *	4.89 (1.55) *
	ADDS	42.6 (22.51)	4.94 (7.69) *	1.4 (1.51) *
	MRS-sedation	54.27 (15.02)	26.40 (16.57)*	29.11 (16.07)*
	MRS-discontent	30.33 (13.65)	18.06 (9.25)*	24.86 (13.48)*
	MRS-anxiety	29.02 (16.04)	25.06 (17.96)*	28.05 (16.21)*
	BSS- cognitive	41.48 (18.02)	10.52(13.52) **	12.36 (12.49)**
	BSS-perceptual	34.89 (14.47)	3.58 (5.97)**	4.98 (5.31)**
	BSS-somatic	35.12 (15.52)	5.94 (9.63)**	3.18 (3.43)**
DAY 3	SSQ	10.67 (7.98)	7.75 (5.26)	5.50 (4.50)
	ADDS	4.22 (4.64)	0.94 (1.48)*	0.7 (1.1) *
	MRS-sedation	27.55 (17.54)	24.18 (16.19)	31.71 (22.81)
	MRS-discontent	27.76 (17.11)	24.10 (16.58)	21.40 (16.23)
	MRS-anxiety	27.76 (17.11)	24.10 (16.57)	23.2 (19.31)
	BSS- cognitive	7.13 (10.17)	6.52 (9.59)	9.23 (8.19)
	BSS-perceptual	2.94 (5.09)	1.75 (3.53)	2.58 (3.42)
	BSS-somatic	4.08 (6.05)	4.01 (4.91)	3.04 (4.31)
	PDI – Total	54.6 (34.51)	20.25 (24.14) *	13.2 (18.51) *
	BIS-10 – Total	63.50 (8.15)	57.18 (12.42)	42.08 (10.51)**
	BIS- 10- cognitive	20.16 (3.20)	18.41 (4.51)	14.23 (5.05) **
	BIS-10 –motor	23.29 (3.73)	21.18 (5.05)	14.15 (3.98) **
	BIS-10- non-planning	19.94 (2.73)	17.59 (4.37)	12.54 (2.87) **

Table 7.4 : Subjective ratings in ketamine users, poly-drug users, non-drug users, * $p<0.01$; ** $p<0.001$

7.7.3.4 Bodily Symptoms Scale : There were higher levels of symptoms in the ketamine groups on all the three bodily symptoms factors on day 0 but no differences on day 3 [Kruskall-Wallis: somatic = 19.30 $p<0.001$; perceptual= 24.60 $p<0.001$; cognitive= 16.61 $p<0.001$].

7.7.3.5 Peters delusion inventory (PDI): Analysis of the total score showed a significant difference between the three groups [$F(2,47) = 11.96$ $p<0.001$] with scores being higher in the ketamine group than the other two groups.

Barratt Impulsivity Scale (BIS): There was a significant difference between the groups for the BIS total score [$F(2, 47) = 16.18$ $p<0.001$] this reflects greater scores in drug users than non-drug using controls [$t(47) = 5.37$ $p<0.001$].

7.8 Discussion

This study investigated response inhibition after an acute dose of ketamine in healthy volunteers and response inhibition and salience attribution in ketamine and poly-drug users and non-drug users. It piloted a novel task designed to examine these two processes. The main findings on day 3 were of an attentional bias to incentive stimuli in non-drug users but not in drug users. In addition, drug users made fewer errors to drug stimuli compared to non-users. Ketamine users made fewer errors to ketamine stimuli and non-illicit drug (alcohol) using controls made fewer false alarms to alcohol stimuli Apart from the above, there were no other differences in response inhibition in drug users compared to non-drug users on day 3. On day 0, there may have been evidence for response inhibition impairments in ketamine users but this is more likely a general performance decrement. Acute ketamine resulted in participants making fewer hits on the Go/No-go task in the high dose group.

7.8.1 Salience Attribution

Non-drug users demonstrated an attentional bias to incentive words i.e. food, sex and money, as shown by there faster response to these words than to other word categories, however there was no evidence of this bias in drug users. Whilst these are preliminary findings from a pilot study and hence must be viewed with caution, these results may reflect the 'undervaluing' of alternative reinforcers in drug users suggested by Goldstein and Volkow (2002). The attentional bias shown to non-drug incentive stimuli

in this study has been shown before in a dot-probe task with food-related stimuli in hungry individuals (Mogg et al., 1998). As far as we are aware, however, this is the first study to directly compare responses to non-drug incentive and drug incentive stimuli in the same task. Again with the caveat that this was only a pilot study, it is possible that these findings may suggest a reduction in attentional bias to non-drug incentive stimuli in drug users compared to non-drug users. If further work confirms this lack of attentional bias to incentive words in drug users, then it is likely, as no ketamine specific effects emerged, that this effect was due to other drug use in this population, including MDMA and cocaine, and possibly interactive effects of using a combination of drugs. The reduction in salience of incentive or 'naturally' reinforcing stimuli could possibly be as a result of changes in the dopaminergic system as a result of drug abuse. It may be that even recreational drug users become used to the immediate pleasure associated with drug taking and thus become less interested in other rewarding activities, however this is purely speculative.

Contrary to our hypotheses, ketamine users did not show any attentional bias to ketamine stimuli and those who used no illict drugs did not show a bias to alcohol stimuli. This is also not consistent with the notion of Robinson & Berridge (2000) that drug stimuli can grab the attention of drug users. A possible reason may be related to the previous findings that alcohol users show attentional bias for alcohol related *pictures* but not *words* (Townshend & Duka, 2001). The latter authors suggest that words may represent more abstract alcohol-related representations as compared to pictures. However pictures were not used as visually ketamine is a white powder which is difficult to distinguish from other white powders used by this poly-drug group, such as cocaine and amphetamine. In addition, the use of written words instead of pictures in the current study may have been of lower ecological validity given this is not the format in which drug users normally encounter drug stimuli. Attentional bias to drug words has been shown in dot-probe tasks previously but only with drug dependent individuals (e.g. cocaine users :Franken et al., 2000). The participants in this study were recreational drug users and as such are likely to have a lesser attentional bias to drug stimuli than addicts. The findings of the current study, taken together with previous

work could possibly suggest that en route to drug dependence, initially the salience of other rewarding stimuli decreases, and then gradually the salience of drug stimuli increases to exceed that of other environmental reinforcers. However, this is highly speculative and further work with individuals of differing levels of drug dependence is needed to clarify this. In addition, this task was more complex that the dot probe paradigm used previously to assess attentional bias. Possibly inhibiting a category of words concurrently to processing another may produce an interactive effect which masks attentional bias.

7.8.2 Response inhibition and impulsivity

Acutely, when administered to healthy volunteers, ketamine did not decrease response inhibition as predicted. The number of hits was reduced in the high dose ketamine group. This may represent either decreased vigilance or a form of 'over-inhibition'. Decreased vigilance is unlikely as previous studies have demonstrated intact vigilance following an acute dose of ketamine on tasks such as the 0-Back (Chapter2; Adler et al., 1998). A more plausible explanation may be that participants were aware of an impairment in functioning and hence were 'overinhibiting' responses to compensate for this. The finding of intact response inhibition on this task of simple pre-potent responding indicate that previous findings of response inhibition impairments on the Hayling task (Chapter 6) do not reflect a general ketamine-induced response inhibition deficit. The Go/No-go taps the inhibition of a simple pre-potent motor response whereas the Hayling task requires the generation of a contextually irrelevant alternative for successful performance. It may be that deficits on the Hayling task relate to the semantic processing impairments described in Chapter 4. The impairment in controlled semantic processing reported in this could lead to an inability to adequately assess the contextual relevance of a semantic alternative. Thus the deficits reported in Chapter 6 may reflect semantic abnormalities rather than a response inhibition impairment.

In Experiment 2, the investigation of acute on 'chronic' effects, the pattern was different from that observed in healthy individuals in the laboratory following an acute dose of ketamine. On day 0 the ketamine group made more false alarms but also less

hits on the Go/No-go task than the non-drug and poly-drug groups. Due to the lower levels of hits on this task (i.e. response initiation) the finding must be interpreted with caution. It could be that the ketamine group are exhibiting a ketamine-induced response inhibition impairment. The reduced number of hits may represent overcompensation upon error detection. The ketamine users also had faster reaction times than non-drug users, which would not be expected given that ketamine is a sedative drug. Therefore the reduced number of hits could reflect a speed/accuracy trade off on the part of the ketamine users. The non-selective nature of the deficits makes these findings difficult to interpret and it is plausible that acute ketamine-induced impairments of working memory, attention and other cognitive systems may also impact on performance. The doses of ketamine reportedly taken by users on day 0 were much higher than those that have been administered in the laboratory. Given the established dose-response nature of ketamine-induced cognitive impairments it is possible that at a lower dose selective response inhibition impairments may have been evident, however the findings from Experiment 1 would seem to suggest this is not the case. There were no differences in response reversal both on and off drug between ketamine users, poly-drug controls and non-drug users. It may be that the reversal load of the task in the current study was not large enough to show differences between the groups.

On day 3 when the ketamine group were drug-free, there were no differences between the three groups in simple motor inhibition as indexed by the number of false alarms or reaction time to false alarms made on the Go/ No-go task. There were no differences in the number of hits or RT to hits which indicates that neither the ketamine nor the poly-drug control groups had difficulties in initiating or inhibiting their responses on this task when drug-free. In addition, there was no main effect of group on the number of errors on the Drug Go/No-go task, again indicating no differences in response inhibition between drug users and non-drug users.

This is contrary to our hypotheses that impaired response inhibition may be associated with recreational drug users', in particular ketamine users', desire to take a drug repeatedly. Response inhibition deficits have been observed in drug dependent

individuals who are currently drug free (e.g Fillmore & Rush, 2002b) with the same task as used in the current study. On the basis of self-ratings of impulsivity (e.g. McCann et al., 1994) and less widely validated measures (e.g. M.Morgan, 1998), the notion that recreational drug users demonstrate poorer response inhibition than non-drug using controls has been largely accepted. Although this was a null finding, and hence we should be caution in out interpretation; the findings would suggest that response inhibition impairments are not evident in these recreational drug users. It may be that these are subtle effects requiring a larger sample size before they can be revealed, or that the particular task was not sensitive enough to detect differences. Preserved response inhibition has been found before with this task in recreational ecstasy users compared to cannabis controls (Fox et al., 2001) although this is the first study to examine response inhibition in recreational poly-drug compared to non-drug users. The ketamine group in this study was composed of relatively light users (2-3 times a month) compared to previous studies where participants have taken ketamine 3-4 times per week (Curran and Monaghan, 2001). It would be interesting to investigate whether response inhibition deficits are present in people with more problematic drug use i.e. heavier ketamine users. Possibly the development of response inhibition deficits that are evident on this task may be one marker of the transition between recreational drug use and drug dependency.

There were differences between the non-drug and drug groups on day 3 on self-rated trait impulsivity. Both drug using groups rated themselves as more impulsive than their non-drug using counterparts, replicating other studies of impulsivity in drug users (M.Morgan, 1998). This is interesting given the lack of differences in response inhibition on day 3. However, it is likely that behavioural and subjective ratings assess different aspects of impulsivity.

7.8.3 Response Inhibition and Salience attribution

The findings from the Drug Go/No-go task are contrary to our hypotheses that ketamine users would make more false alarms to ketamine stimuli and non-drug users to non-drug incentive stimuli. Ketamine users actually made the least false alarms to ketamine

stimuli and the non-drug (alcohol) users made the least false alarms to alcohol stimuli. It is possible that an attentional bias towards a certain stimulus may in fact confer some kind of advantage in terms of response inhibition errors, making the subject more able to discern the drug-related stimuli from other less salient stimuli and hence more able to inhibit responses. However, this is not supported by the reaction time data that suggest that there is no attentional bias to drug stimuli in ketamine users or alcohol stimuli in alcohol users. Again it may be that due to the complexity of the task, an interaction of effects is occurring. Further work is necessary to tease apart the exact processes occurring. It may also be that as the drug users included in this study were not drug dependent, they are practised in exercising response inhibition for drug stimuli and the same may apply to the non-drug alcohol users. In addition, an inevitable pitfall of our design is that the ketamine groups were more familiar with the 'drug' words, so perhaps this is why they made less false alarms to these stimuli. Controlling for word frequency for these stimuli in these populations is clearly impossible as the ketamine users encounter ketamine words far more often. Thus perhaps these findings are the result of a word frequency confound. However, all groups should be equally familiar with the alcohol stimuli so this cannot account for the finding of better response inhibition in the non-drug groups to these stimuli. Finally, it may be that the inhibition of a simple preotent motor response may be highly different from the 'real-world' scenarios in which response inhibition deficits in drug users occur.

This is the first study to demonstrate higher levels of delusional thinking (PDI) amongst ketamine users compared to non-drug and poly-drug controls. Some previous studies with ketamine users have found elevated levels of schizotypal symptoms (Curran & Morgan, 2000; Chapter 5 / Morgan et al., 2004c) but ketamine users have not been assessed on delusional ideation previously. Further work is needed to clarify the exact nature of the pre-existing or persisting schizophrenia like effects associated with chronic ketamine use.

7.8.4 Methodological considerations

As with all recreational drug user studies, there were several limitations inherent in testing the population in Experiment 2. Amongst studies of poly-drug users a strength of this research was the use of both urine tests and subjective reports to verify the drug use of participants, therefore we could verify that ketamine was taken on day 0 and subjective effects again served to confirm this. The drug histories taken from participants were not verified objectively as hair analysis was beyond the resources available for this study. All the poly-drug controls and all but one of the ketamine group tested positive for cannabis at follow-up. None of the participants reported smoking cannabis between day 0 and day 3. As cannabis is detectable in urine for up to 21 days after acute use, its presence on day 3 in the urine of these poly-drug users is not surprising.

There were also some limitations associated with the non-drug using control group. Ideally the group would not have used any psychoactive substances. As it was impossible to find non-drug users from the same social demographic as the other groups who did not drink, it was necessary to include regular alcohol drinkers. Furthermore, 6 of the non-drug users had tried cannabis on a maximum of 3 occasions. All of these 'non-drug users' had abstained for over a year and none tested positive for cannabis. It may have been possible to find non-drinking controls who had never tried cannabis, however the authors felt it was more important to control for social background than to find a completely non-drug using group from a different setting.

In relation to the novel Drug Go/No-go task, one disadvantage (and yet also advantage) was that it was relatively complex and theoretically aimed at tapping multiple processes (response inhibition and salience attribution and their interaction). It is possible that other processes than salience attribution and response inhibition were influencing performance. However, the task is based on standard Go/No-go procedures used to test response inhibition. It was not clear whether these words were acting as true incentives or 'motivational magnets' (Berridge & Robinson, 2003) but concurrent skin conductance recording might help to clarify this. As discussed above, another limitation

is that ketamine users were inevitably more familiar with ketamine related words than non-drug users. To overcome this participants were shown the words beforehand. However this may in turn have created a working or episodic memory component to the task if participants tried to remember words in each category. Furthermore words were only repeated three times in the task which set constraints on the number of stimuli we were able to use. This was to try and ensure that words were being processed semantically and not perceptually, as may happen if words are repeatedly presented. However the low number of stimuli could have reduced the power of the task to detect effects. In retrospect we accept that the task may have been somewhat ambitious. It would have been better to use a simpler task, for example to examine salience attribution we could have used a dot probe that examines drug stimuli paired with incentive stimuli, perhaps with the use of pictures instead of words.

In summary, this study examined response inhibition, in healthy volunteers following an acute dose of ketamine and findings suggested an 'over-inhibition' of responding, contrary to hypotheses. The current study additionally investigated response inhibition and salience attribution in ketamine users compared to poly-drug users and non-drug using controls. We found no evidence of impaired response inhibition in ketamine users or recreational drug users in general compared to alcohol using controls. Our novel salience Go/No-go had some success in discerning both drug users from non-drug users and ketamine users from non-ketamine users. In terms of salience attribution, there were indications that the non-drug group were attributing primary salience to natural incentive stimuli (e.g. food) whereas the drug users did not. However, contrary to our expectations, the drug users did not demonstrate any attentional bias to drug stimuli and actually instead of being impaired, showed better response inhibition overall to drug stimuli. The ketamine users demonstrated improved response inhibition for ketamine words and the alcohol (i.e. non-illicit drug) users for alcohol words. This paradoxical effect may reflect a combination of attentional bias and /or compensatory mechanisms that maintain these users as recreational drug-using, rather than drug dependent, individuals.

Chapter 8: Me-pulse inhibition

A novel self-monitoring task piloted in high schizotypy scorers, healthy volunteers following an acute dose of ketamine and ketamine users

"If the doors of perception were cleansed everything would appear to man as it is, infinite..." William Blake

8.1 Overview

Previous work has demonstrated that the intensity of a perceived stimulus is lower for an identical stimulus when one generates it oneself compared to if it is externally generated. Externally produced sensory events are thought to be distinguished from internally generated stimuli on the basis of knowledge of one's intentions and motor commands. Deficits in this form of self-monitoring have been proposed to underlie symptoms such as hallucinations and delusions in schizophrenia and there is some evidence to support this claim. This study set out to develop a novel paradigm – 'Me-pulse' inhibition - to investigate self-monitoring in psychopharmacological studies based on the question 'Can one startle oneself?'. Three populations were used to pilot the Me-pulse inhibition task: a) 10 high and 8 low scorers on the O-LIFE schizotypy scale (*Experiment 1*); b) 8 healthy male volunteers administered either 200ng/ml target controlled infusion of ketamine and placebo in a within subjects design (*Experiment 2*); and c) 12 recreational ketamine users and 11 poly-drug controls (*Experiment 3*). All received acoustic stimuli binaurally and the eyeblink component of the startle response was measured by recording EMG activity from the orbicularis oculi muscle. Three types of stimuli were administered. Participants either i) heard the startling stimulus alone ii) heard a prepulse (lead interval of 450msec) which preceded the startling stimulus (active attention prepulse inhibition - PPI) or iii) were given a signal to press a button to generate the startling stimulus themselves (Mepulse inhibition - MePI). In Experiment 1, there were no group differences in PPI but significantly lower MePI in

high schizotypes. There were no differences between PPI following ketamine or placebo (Experiment 2) but there was a trend for lower MePI on ketamine. In Experiment 3, there was lower PPI in ketamine users than polydrug controls, but no differences in MePI. In high schizotypes and both groups of drug users there was evidence of facilitation of MePI i.e. higher than baseline startle. The Me-pulse inhibition paradigm was sensitive to differences between groups in 3 different populations. These differences may reflect deficits in self-monitoring that underpin some psychiatric symptoms induced by ketamine and observed in high scorers on schizotypy scales.

8.2 Introduction

To avoid sensory overload, humans must select, screen, process and organise important information from the " one great blooming, buzzing confusion" (James, 1890, pp.445) that is the world. It is important that our sensory systems discard or 'gate out' trivial stimuli so we may focus attention on the most important changes in our environment. However, in certain cases this screening process may go awry. In the popular media, psychedelic drugs, such as LSD, have long been viewed as disrupting the normal flow of information in and out of the senses (e.g. Huxley, 1954) and more recently schizophrenia has been explained in similar terms (Braff et al. 2001; Frith, 1992; Ford et al., 2001). Researchers have attempted to develop unifying theories to explain the symptoms of schizophrenia, some of which have suggested that failures in gating ingoing sensory information (i.e. 'input') lead to cognitive fragmentation, sensory overload and thought disorder (McGhie & Chapman, 1961; Braff, 1993). Others propose that disruption of the monitoring of outgoing information such as speech and other motor actions (i.e. 'output') deficits (e.g. Frith, 1992) underlie symptoms such as hallucinations and delusions of control. Ketamine is a psychedelic drug that can induce the schizophrenic symptoms described above (Krystal et al., 1994). It therefore seems possible that underlying the symptoms induced by ketamine there may also be deficits in monitoring the 'input' or 'output' of sensory information.

The origin of 'input' deficit theories of schizophrenia is the common complaint amongst schizophrenics that they are unable to prevent irrelevant thoughts and sensory stimuli from entering awareness. The 'gating' of incoming sensory information has been examined in schizophrenia using the prepulse inhibition (PPI) paradigm (for reviews see Braff et al., 2001; Geyer et al., 2001). As discussed in Chapter 1, PPI refers to the inhibition of the startle reflex associated with a sudden intense stimulus when it is preceded by a weak sensory stimulus (i.e. the prepulse). It has been suggested that PPI is protective, in that it occurs to ensure that the prepulse can be adequately processed without interference from subsequent events including the startling stimulus (Braff et al., 2001; Blumenthal, 1996). In this way it is thought that the 'gating' is functional to

an organism as it helps to prevent sensory overload in a world where we are constantly bombarded with stimuli (Braff & Geyer, 1990). Schizophrenic patients in general exhibit reduced PPI independent of the modality of stimuli (e.g. (Kumari et al., 2000; Braff et al., 1978). Further, PPI is relatively unaffected by antipsychotic medications in either humans (see Braff et al., 2001 for a review) or animals (see Geyer et al., 2001 for a review).

Anecdotally, participants on ketamine like schizophrenics, report difficulties in stopping thoughts and sensory stimuli popping into their heads. Studies examining ketamine's effects on PPI have produced equivocal results: enhanced PPI (Abel et al., 2004; Duncan et al., 2001); reduced PPI (Umbricht et al., 2001) and no effect (van Berckel et al., 1998). However, the above studies were all passive attention paradigms that less robustly elicit PPI in schizophrenia than active attention paradigms (Dawson et al., 1993). Further all differed in the actual dose of ketamine and PPI paradigm used. It may also be that 'input' deficits do not account for the symptoms induced by ketamine.

Output theories suggest that an inability to distinguish between self generated and externally generated stimuli is involved in the positive symptoms of schizophrenia (Frith, 1992). It is often valuable to 'gate out', or at least reduce in intensity, stimuli which arise as a consequence of our own actions (Blakemore et al., 1999). Self-generated stimuli (e.g. one's own voice) are evolutionarily generally of a lesser survival importance than externally generated events (e.g. the roar of a predator). Several theories postulate that externally produced sensory events are distinguished from internally generated stimuli on the basis of knowledge of our intentions and motor commands (Jeanerrod, 1988; Decety, 1996). It is thought that some form of central self-monitoring system may anticipate the results of actions and therefore discern them from externally generated stimuli (Frith, 1992; Wolpert, 1997). Previous studies have indeed shown that the intensity of a perceived stimulus is lower for an identical stimulus when a subject generates it themselves compared to one that it is externally generated. One study looked at auditory evoked potentials (AEPs) recorded from the scalp and found that when an individual triggered a noise themselves, the resulting AEPs were of

shorter latency and decreased amplitude than when the noise was externally triggered (Schafer & Marcus, 1973). The authors termed this the 'self-generation' effect. In an elegant study, Blakemore and colleagues (1999) re-examined the phenomenon first noted by Weiskrantz et al. (1971) that people are unable to tickle themselves. In their study increasing the discrepancy between the predicted and actual consequences of self-generated tactile stimuli increased their perceived 'tickliness'. This suggests that the inability to tickle oneself occurs as a result of a prediction made by the motor system (or an 'efference copy'). However, when Blakemore et al. (2000) compared 'tickliness' in patients with delusions of control and auditory hallucination with controls, the clinical sample rated self-produced sensations as similar to those generated by external agents. In addition, schizophrenic patients with hallucinations were more likely to attribute their own distorted voice to external sources than non-hallucinators or psychiatric controls(Johns et al., 2001) and were less able to identify their own, rotated drawings than healthy or non-psychotic psychiatric controls (Stirling et al., 1998). Thus there is some evidence support the theory that auditory hallucinations and passivity experiences are associated with a defect in monitoring 'output' or self-monitoring.

Anecdotally, many of the participants in the acute ketamine studies described in this thesis reported the sensation that they were not in control of their actions e.g. "... moving was like I was, like, a robot, like a puppet on strings..." (participant 8-Semantic priming study) which is reminiscent of delusions of control. As discussed above, this is thought to occur as a result of a failure to monitor one's own actions i.e. output. So it seems possible that following acute ketamine administration a disruption to the self monitoring system occurs. However the existing self-monitoring tasks that have been used in schizophrenia such as tickling and drawing are inappropriate to test this because of the analgesic and motor effects of ketamine. Thus it was necessary to design a new task which we based upon the question, "Can one startle oneself?"

Whether one can startle oneself has not been previously examined. However (Schafer & Marcus, 1973; described above) showed that AEP responses to self-evoked auditory stimuli were attenuated compared to those generated by the experimenter. This

reduction in AEP might suggest that there is a similar attenuation of responding due to an efference copy (i.e. a prediction of the sensory consequences of an action) produced in conjunction with a central monitoring system similar to that hypothesised to be involved in the suppression of ticklishness. Therefore we designed a new paradigm, based on an active attention version of pre-pulse inhibition, to include self-generated startling stimuli ('me-pulses') along with prepulses and startling stimuli. Thus in this task the startling stimulus will be one that is *triggered by the participant* in addition to the one that occurs following the prepulse. By examining responses to self-generated startle, we were also able to measure any reduction in response objectively by recording facial electromyographic (EMG) activity.

Whilst our aim was to examine 'mepulse' inhibition following acute ketamine, it was necessary to first pilot the paradigm to examine whether it was sensitive to schizophrenic-like differences. Whilst ideally we would have piloted the study with patients with schizophrenia, this was beyond the scope of the study. However it is not only schizophrenic patients who demonstrate delusional or hallucinatory thinking and experience perceptual aberrations such as those described above. Within the 'normal' population many individuals will experience something akin to a schizophrenic experience at some point in their lifetimes. For example, most people at some point will turn around because they think someone has said their name, only to find that there is no-one there. Some have argued that, rather than a discrete, diagnostic category, the concept of schizophrenia should be redefined as symptoms occurring on a *continuum* (Claridge, 1987; Chadwick et al., 2005). This notion of a continuum of schizophrenic symptoms has been termed schizotypy: at one end are individuals who experience full-blown psychotic symptoms, whilst further along the continuum are healthy individuals who have personality traits that mark a proneness to psychosis e.g. believe in telepathy or magic. The concept of schizotypy has been shown to have validity in that healthy volunteers with high scores on schizotypy scales demonstrate poorer performance on tasks upon which schizophrenic patients themselves exhibit deficits (Peters et al., 1994; Claridge, 1994). In addition, individuals with high schizotypy scores are at a greater risk of developing a schizophrenic illness (Chapman & Chapman, 1987).

Similarities between schizophrenia and schizotypy, have prompted a body of research that has utilised individuals assessed on schizotypy scales to investigate psychosis. The advantages of this line of research are that they circumvent several confounding variables common to research with schizophrenic patients i.e. long hospitalisations, medication, generalised performance deficits and varying levels of premorbid functioning. PPI has been examined in schizotypy before but with somewhat conflicting results of either no effect (Cadenhead & Braff, 1992; Lipp et al., 1994; Abel et al., 2004) or reduced PPI (Simons & Giardina, 1992; Cadenhead et al., 1993). The only research that has examined an active attention PPI paradigm as we intended to examine in this study found reduced PPI in individuals experiencing high levels of magical ideation compared to normals (Schnell et al., 1995).

Self-monitoring deficits as discussed, have been extensively investigated in schizophrenia but little research has examined their prevalence in psychosis prone individuals. Given that these individuals experience perceptual distortions and often have mildly delusional beliefs, according to Frith's (1992) theory, they may exhibit some deficits in the monitoring of their own actions. Thus we decided to pilot our novel task in this population (Experiment 1). Following this we intended to examine self-initiated startle following an acute dose of ketamine in healthy volunteers (Experiment 2) and finally we wished to examine the effect of chronic ketamine use in a population of substance users on performance on the same task (Experiment 3). Based on the findings of Schafer and Marcus (1973) it was hypothesised in Experiment 1 (pilot study) that individuals who are low in schizotypy will show a decrease in startle response to self-triggered stimuli, but individuals who are high in schizotypy will *not* show a decrease in amplitude of response. If high schizotypy individuals show a startle response to self- triggered stimuli which is just as great as that shown in response to randomly generated stimuli, then it can be said that they show the propensity to startle themselves. This would provide further support for the notion that schizophrenic-like symptoms derive from defective self-monitoring (output deficits). No previous research has addressed issues of self-monitoring with acute or chronic ketamine, so no specific

predictions were made for experiments 2 & 3. However, given the anecdotal reports of altered monitoring experiences under the influence of acute ketamine, we speculated that the drug would induce a similar pattern to that found with high schizotypes.

An additional benefit to using this paradigm was that we were able to use an active attention PPI paradigm to look at perceptual gating deficits, as well as examining 'me-pulse' inhibition (hereafter MePI). Thus the study attempted to address existing controversies related to the idea that perceptual gating deficits only appear in schizophrenia patients *versus* the suggestion that in fact perceptual gating deficits appear in healthy volunteers who are high in schizotypy, and as such represent a trait marker for schizophrenic illness. More inhibition was found at 120 ms lead interval in an active attention paradigm in normals compared to individuals experiencing high levels of magical ideation (Schnell et al., 1995). Thus we predicted that in our study the high schizotypes may show impaired PPI. No previous study has examined active attention PPI following an acute dose of ketamine, or any form of PPI following chronic ketamine use. So whilst the paradigm was not designed specifically for examination of PPI, this was also possible.

Experiment 1: Mepulse and prepulse inhibition in high and low schizotypes: a pilot study

8.3 Method

8.3.1 Participants and Design

An independent group design was used to compare individuals who had high schizotypy scores with individuals who had low schizotypy scores. Participants were recruited through advertisments or via a database of volunteers for psychological research. Inclusion criteria required participants to be aged between 18 and 30 years, to have no serious mental illness or history of one, not taking any psychoactive medication, have no hearing impairment or any history of head injury. After completing an email version of the O-life questionnaire (Mason et al., 1995 described below), only those whose total schizotypy (STA) score fell *either* below 10 points *or* above 24 points were recruited (2 standard deviations away from the mean in a previous study, Beford

et al., submitted). In addition, as the PPI response of women fluctuates over the menstrual cycle, female participants were required to participate in the experiment during the first four days of their period (see Swerlow et al., 1997).

8.3.2 Procedure

Participants gave written, witnessed informed consent on the day of testing, and then their demographic data were recorded.

8.3.3 Assessments

The O-life Questionnaire (Mason et al., 1995): This 159 item self-report questionnaire yields a total schizotypy score (STA) and scores on four dimensions of schizotypy (as identified by Claridge et al., 1996) as follows:

1) Unusual experiences - unusual perceptual events, hallucinatory experiences, and magical thinking.

2) Cognitive Disorganisation - difficulties in sustaining attention and concentration, as well as moodiness and social anxiety.

3) Introvertive Anhedonia - difficulties gaining enjoyment from social, or other sources, a lack of enjoyment of physical and emotional intimacy, and a preference for spending time alone. These items are thought to relate particularly to the 'negative signs' of schizophrenia.

4) Impulsive Nonconformity - asocial behaviours, impulsivity and non-conformity.

'Me–pulse' inhibition

Participants were seated in a comfortable chair. The area around each subject's right eye was cleaned with an alcohol swab and then two miniature (4mm) Ag-AgCl electrodes were positioned over the orbicularis oculi muscle, approximately 5mm below the right eyelid, one directly below the pupil and one approximately 1 cm lateral to the first. The third (ground) was placed in the centre of the forehead. Eyeblinks were recorded as EMG activity using an EEG-8 bioamplifier (Psylab, UK) and digitised for later analysis. EMG activity was filtered with a 30 Hz high pass filter, a 500 Hz low

pass filter and a 50 Hz hum-notch filter and recorded at 1KHZ for 250ms from the onset of the startle stimulus. Acoustic stimuli were calibrated with a sound level meter (Realistic) and consisted of 40ms bursts of 116db broadband noise with an instantaneous rise time over continuous background noise of 50db presented bi-aurally through headphones (Technics). The prepulses were 20ms duration noise bursts of 80db , i.e. 30db above background noise presented 430 msec before the pulse. Although not optimal for PPI, this lead interval was used because it was the mean time to respond with a button press to a green square in 20 volunteers. This was an attempt to make the delay between prepulse and pulse as similar as possible to the delay between 'mepulse' i.e. the cue prompting participant to initiate the pulse. The mepulse was a green square presented centrally on a VDU. After a five minute acclimatisation period with the background noise (50db) the first block of six 116db 40ms noise bursts was presented (pulse alone). These pulse alone trials were followed by the four blocks of 12 trials each: 4 pulse alone trials, 4 prepulse trials and 4 mepulse trials. The final block was identical to the first, consisting of six pulse alone noise bursts. The total session included 48 trials. Participants were seated throughout testing and asked to fixate upon the computer screen and press a button on a pad when they saw a green square on the screen. Responses that fell outside the physiological range for a reflex blink (20ms or beyond 90ms) were discarded. Responses were recorded as startle magnitudes, peak latencies and percentage MePI/PPI as differences in absolute μv units are correlated with baseline startle amplitude.

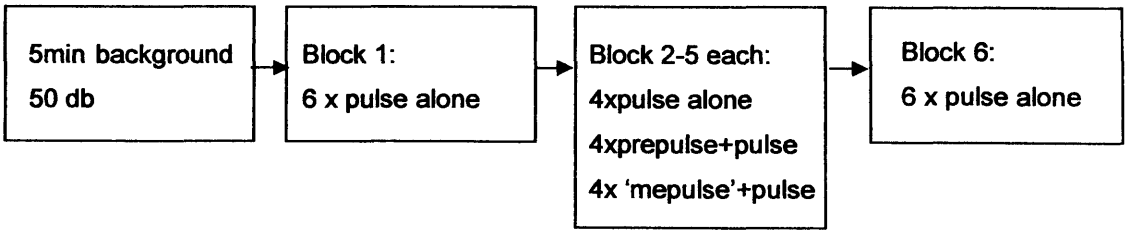


Figure 8.1: Schematic of the me-pulse task.

8.3.4 Statistical Analyses

Habituation and overall startle magnitude was examined by comparing startle responses on Block 1 with startle response on Block 6 in a RMANOVA with Group (High or Low schizotypy scorer) as a between subjects factor and Block (1 or 6) as a within subjects factor. Percentage Mepulse inhibition (MePI) was calculated with the data from trails 2-5, using following formula [100 * (total startle magnitude pulse trials – total magnitude mepulse trials) / total startle magnitude pulse trials] and prepulse inhibition was calculated using the same formula but substituting prepulse data for mepulse. This was analysed as a 2 x 2 repeated measures, with Group (High or Low schizotypy) as a between subjects factor and Type of trial (Prepulse or Mepulse) as a within subjects factor. Given this was a new task and it was not clear how independent these processes were, separate Oneway ANOVAs were also run for the mepulse and prepulse data separately. Demographic data were analysed using t-tests, Chi-Squared analyses and where non-parametric, Mann-Whitney U tests. Correlations were conducted between schizotypy sub-factors and the percentage mepulse inhibition and prepulse inhibition. Non-significant main effects and interactions were not reported.

8.4 Results : Schizotypy groups

8.4.1 Demographics

10 participants had a total STA score of < 10 and formed the low schizotypy group (3 males mean age: 24.10 ± 7.92; 1 smoker;) , 8 had a total STA score >24 and were entered in the high schizotypy group (3 males; mean age 27.5 ± 10.76 years; 2 smokers). There were no differences in age or gender. Schizotypy data are given in Table 8.1 below.

8.4.2 Me-pulse task

8.4.2.1 Startle Magnitude and habituation (See Table 8.2)

2 x 2 RMANOVA demonstrated a significant main effect of Block [$F(1,16)= 4.55$ $p<0.05$] which reflects a decrease in startle magnitude between Block 1 and Block 6

(i.e. habituation occurred). The trend [F(1,16) = 3.47 p=0.082]for group difference reflects higher levels of startle in the low compared to the high schizotypes.

	High schizotypy (n= 8)	*Low schizotypy (n=10)*
Total STA score	27.25 (4.20)	6.40 (2.27)
Total score for unusual experiences	19.25 (4.71)	2.89 (2.15)
Total score for cognitive disorganisation	19.00 (5.07)	4.67 (4.33)
Total score for introvertive anhedonia	10.75 (4.37)	4.33 (5.77)
Total score for impulsivity	10.14 (2.85)	5.78 (2.86)
Total score for SPQ	8.5 (5.08)	47.25 (14.02)
SPQ Cognitive factor	2.70 (3.12)	14.63 (5.40)
SPQ Interpersonal factor	3.0 (2.71)	20.25 (7.09)
SPQ Disorganised factor	2.80 (1.75)	12.38 (3.78)

Table 8.1: Mean (s.d.) scores in the high and low schizotypy groups on schizotypal symptoms.

	High schizotypy n=8	Low schizotpy n=10
Block 1 startle magnitude, μv	15.21 (16.63)	45.81 (52.10)
Block 6 startle magnitude, μv	7.19 (12.23)	22.47 (21.27)
Peak latency, msec	61 (31)	74 (61)

Table 8.2: Startle magnitude and peak latency in the high and low schizotypy groups

8.4.2.2 Percentage Me-pulse/ Pre-pulse inhibition

Although a RMANOVA demonstrated no main effects or interactions, a oneway ANOVA showed a significant difference between the groups in mepulse inhibition [F(1,16)= 8.25 p=0.012], which is a result of an increase in startle response to self-generated stimuli in the high schizotypy subjects compared to pulse alone, and a decrease in the low schizotypy subjects (See Fig 8.2). Mean reaction times to generate the mepulse did not differ significantly from the prepulse lead interval.

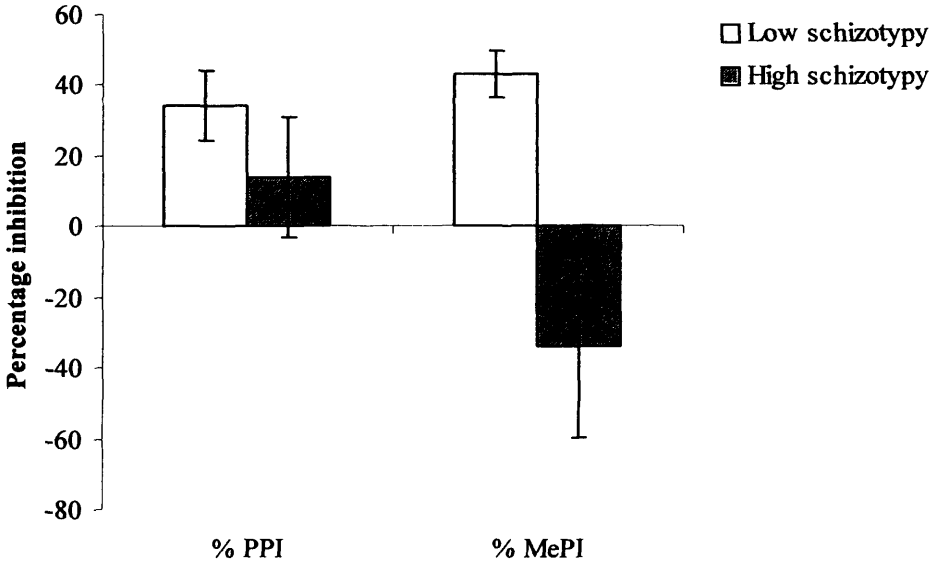


Figure 8.2: Percentage prepulse (%PPI) and mepulse (%MePI) inhibition across schizotypy groups.

There were no differences in the percentage of inhibition in the mepulse and prepulse conditions in the low schizotypes.

8.4.2.3 Peak latency

There were no group differences in peak latency.

8.4.3 Correlations

There were significant negative correlations between percentage MePI and the schizotypy subscales of Cognitive disorganisation [r = -0.538, p=0.032] and Introvertive anhedonia [r =-0.507 p=0.045].

Experiment 2 – Effects of acute ketamine on mepulse and prepulse inhibition in healthy volunteers

8.5 Method

8.5.1 Participants and design

A crossover design was used to compare ketamine (200ng/ml) with placebo. Treatment order was balanced across subjects. The washout period between treatments was 2 –7 days (mean 7.2 ± 3.65 days). 11 male participants were recruited into the study. They were screened using the procedures described in chapter 2, in addition to the criteria given in the previous experiment above. 2 participants with negligible baseline startle responses were excluded and 1 participant only completed one test day. Eight subjects completed both test days.

8.5.2 Drug administration

Participants attended test sessions in the morning having fasted from midnight the day before the study. Participants were cannulated in the non-dominant forearm and a computer controlled intravenous infusion began via a Graseby pump using the Stanpump program (Schafer et al., 1991) to maintain an estimated target plasma concentration of 200ng/ml. Drug administration was double blind, however the psychotomimetic and sedative effects of ketamine meant that treatment condition was apparent to the experimenter and subjects.

8.5.3 Assessments

Mepulse task

The mepulse task used identical methods to those described in experiment 1.

Subjective Effects

Five assessments used previously in this thesis were also administered: ADDS ; MRS; SSQ; Subjective Effects; Spot the Word.

8.5.4 Statistical Analyses

These were parallel to those described in Experiment 1, however instead of the between subjects factor of group, this study had the within subjects factor of Drug (placebo, ketamine). The sub-factors of the schizotypy *state* scale were correlated with perecentage MePI and percentage PPI.

8.6 Results: Acute ketamine

8.6.1 Demographics

The 8 participants in the current study had a mean age of 25.25 (3.19) years and had a spot the word score of 50 (3.82) and had spent 17 (1.77) years in education.

8.6.2 Mepulse task

8.6.2.1 Startle magnitude and habituation

An analysis of startle magnitude for blocks 1 and block 6 found a significant main effect of Block [$F(1,7) = 12.43$ $p=0.039$] indicating habituation had occurred, however there were no main effects of group or interactions (Table 8.3).

8.6.2.2 Percentage prepulse inhibition and mepulse inhibition

A 2x2 RMANOVA with Drug and Trial type as within subjects factors found a trend for a main effect of group $t(7) = 4.06$ $p=0.084$. Further analysis demonstrated a trend for less mepulse inhibition on ketamine compared to placebo [$t(7) = 2.18$, $p = 0.066$] *(Fig 8.3)*

	Placebo	Ketamine
Block 1 startle magnitude, μv	20.70 (15.40)	18.49 (13.47)

Block 6 startle magnitude, μv	8.88 (6.50)	10.72 (8.30)

Table 8.3: Startle magnitude across placebo and ketamine treatment

8.6.2.3 Peak latency

There was no difference in peak latency across the test days.

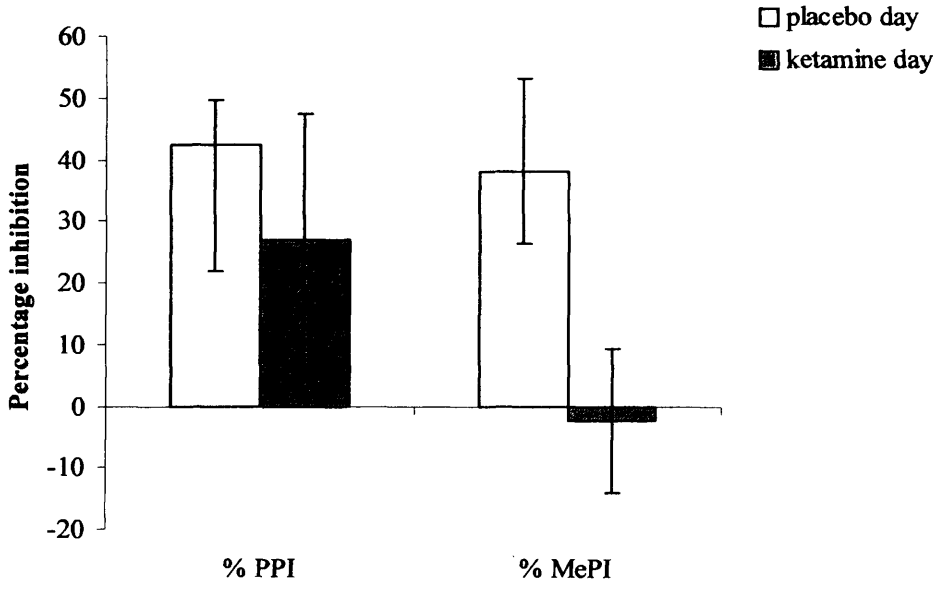


Figure 8.3: Percentage prepulse inhibition and mepulse inhibition across treatment day

8.6.3 Subjective effects

There was a trend for a main effect of day on schizotypal state scores [$F(1,7) = 4.02$, $p=0.085$]. There was a significant increase in dissociation on ketamine [Wilcoxon-Signed Ranks, $Z = -2.54$ $p = 0.012$]. There was a significant effect of Drug on drowsiness [$F(1,7) = 10.09$, $p=0.016$], again with greater drowsiness on ketamine. There was no effect of ketamine on discontentedness or anxiety. There was also a significant increase in somatic [$F(1,7) = 15.81$ $p=0.007$], cognitive [$F(1,7) =10.80$,

p=0.013] and perceptual [F(1,7) = 7.94, p=0.026] symptoms on ketamine compared to placebo (Table 8.4).

	Placebo	Ketamine
ADSS	1.38 (2.77)	14.5 (7.58)
SSQ	6.0 (7.69)	12.75 (4.89)
MRS – Drowsiness	34.73 (14.93)	55.72 (9.94)
MRS – Discontentedness	28.48 (13.39)	28.78 (17.32)
MRS –Anxiety	14.07 (6.60)	10.38 (7.24)
VAS – Somatic	11.00 (11.77)	39.94 (13.71)
VAS – Cognitive	8.69 (10.24)	28.53 (15.53)
VAS – Perceptual	9.75 (10.98)	29.45 (17.62)

Table 8.4: Self-rated symptoms on placebo and ketamine.

Experiment 3: Mepulse and prepulse inhibition in ketamine users.

8.7 Method – Ketamine users

8.7.1 Participants and Design

23 participants completed the study: 12 males and 11 females. As ketamine users are 'poly-drug' users the comparison group were poly-drug controls matched for other psychotropic drug use except ketamine. The age range was 19-45 years [polydrug controls: 21.50 ± 3.20; ketamine group: 23.19 ± 6.31]. There were 4 females in the ketamine group and 7 females in the poly-drug control group. Participants were recruited via volunteer databases, the internet and by snowball sampling (Solowij, Hall, and Lee, 1992). The ketamine group consisted of 12 participants who regularly took ketamine (a minimum of twice a month). The control group consisted of 11 ketamine naïve (polydrug) participants who were broadly matched with ketamine users on recreational drug use apart from ketamine.

8.7.2 Procedure

All participants who met the relevant drug criteria provided written, witnessed, informed consent. An identical battery to that employed in Experiment 1 was used. Additionally, a general drug history was given by the participant, detailing their current and past drug use. Participants were asked to give a urine sample to test for recent drug use (cannabis, MDMA, cocaine, opiates, ketamine and benzodiazepines).

8.7.3 Assessments

Mepulse task: described above
Subjective Effects : SSQ, ADDS, PDI, SES (alldescribed in Chapter 4)

8.7.4 Statistical Analyses

Statistical analyses were similar to those used in Experiment 1. Correlations were conducted between the state schizotypal and dissociative symptoms questionnaires and percentage PPI and percentage MePI.

8.8 Results: Ketamine Users

8.8.1 Demographics and Drug Use

There were no significant group differences in pre-morbid IQ [spot the word score-controls: 49.25 ± 5.16; ketamine: 50.75 ± 4.70], age or gender. There were no significant group differences in the use of cannabis, ecstasy or alcohol (See Table 8.5). The ketamine users had last used the drug a mean of 10.32 ± 9.45 days previously, with a minimum last use of 3 days earlier. Urine screens for both groups were all positive for cannabis but no other drugs of abuse. Other self-reported occasional drug use included cocaine (7 ketamine / 5 controls), amphetamines (5 / 2), valium (2/1), LSD/ mushrooms (6 / 2), and amyl nitrate (2 / 0).

		Ketamine Users	*Poly-drug controls*
Ketamine	Days Per Month	4.17 (2.51)	0.00 (0.00)
	Years Used	1.80 (0.90)	0.00 (0.00)
	Amount Used Per Session (grams)	0.68 (0.56)	0.00 (0.00)
Cannabis	Days Per Month	10.25 (12.06)	10.45 (9.55)
	Years Used	4.58 (3.82)	6.00 (4.22)
	Amount Used Per Session (number of joints)	1.50 (1.31)	1.91 (0.94)
Ecstasy	Days Per Month	4.25 (3.89)	3.18 (5.69)
	Years Used	3.96 (3.25)	3.82 (3.34)
	Amount Used Per Session (tablets)	3.83 (2.37)	3.82 (5.56)
Alcohol	Days Per Month	11.83 (7.72)	17.72 (8.54)
	Years Used	9.00 (6.59)	6.73 (2.97)
	Amount Used Per Session (units)	5.67 (4.77)	6.64 (4.24)

Table 8.5: Patterns of drug use in the ketamine and poly-drug groups

8.8.2 Mepulse task

8.8.2.1 Startle Magnitude

2x2 RMANOVA demonstrated a significant main effect of block [$F(1, 21) = 8.17$ $p=0.009$] but no main effect of group or interaction. The main effect of block reflected a decrease in both groups between Block 1 and Block 6 (i.e. habituation).

	Ketamine users	Poly-drug controls
Block 1 startle magnitude, μv	19.91 (18.79)	20.55 (22.22)
Block 6 startle magnitude, μv	9.17 (8.55)	7.80 (9.61)

Table 8.6 - Startle magnitude across Blocks 1 and 6

8.8.2.2 Percentage prepulse and mepulse inhibition

2 x 2 RMANOVA demonstrated a significant main effect of Trial Type [$F(1, 21) = 5.79$ $p= 0.025$] but no main effect of group or interaction. The main effect of Trial type reflected a lower percentage of 'me-pulse' than 'pre-pulse' inhibition in both groups. In light of the schizotypy data, SSQ scores were entered as a covariate to the data which were reanalysed, however no differences emerged. A post-hoc comparison showed that poly-drug controls exhibited significantly more prepulse inhibition than ketamine users [$F(1, 21) = 8.06$ $p=0.01$]. There was a correlation between dissociative symptoms and percentage 'me-pulse' inhibition ($r = -0.453$ $p=0.03$).

8.8.2.3 Peak latency

There were no effects of group on peak latency.

8.8.3 Subjective effects

There were no significant group differences in subjective effects (Table 8.7).

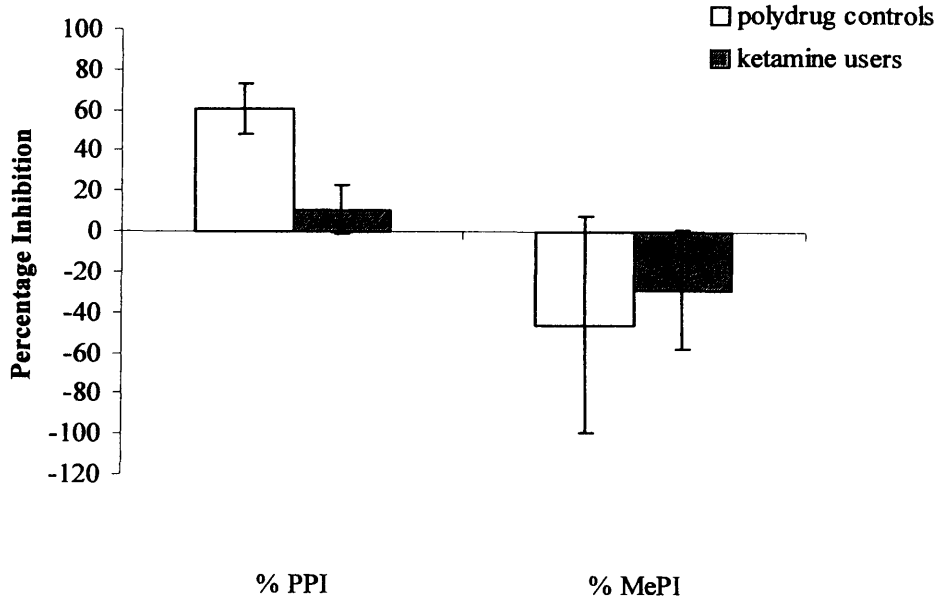


Figure 8.4: Percentage PPI and MePI in ketamine users and poly-drug controls

	Ketamine Users	Polydrug Controls
ADSS	7.38 (10.38)	7.27 (6.46)
PDI	35.53 (3.62)	34.00 (4.46)
SSQ	16.13 (10.01)	15.79 (11.31)
Cognitive symptoms	68.18 (50.54)	55.03 (60.81)
Perceptual symptoms	42.44 (57.14)	50.16 (64.89)
Somatic symptoms	43.40 (60.01)	58.27 (68.37)

Table 8.7: Subjective effects across ketamine users and poly-drug controls

8.9 Discussion

This study set out to examine self-monitoring following acute and chronic ketamine. It used a novel self-startle task that aimed to extend the existing prepulse inhibition paradigm. Experiment 1 piloted the task with high and low schizotypy subjects. Low schizotypy scorers showed inhibition of the startle response both following a prepulse and a self-generated pulse. High schizotypy scorers also showed prepulse inhibition and yet they exhibited facilitation (i.e. greater startle than for pulse alone) for the pulse following the mepulse. In Experiment 2, mepulse inhibition of the startle response was evident on placebo but an acute dose of ketamine tended to reduce this inhibition. There were no differences in prepulse inhibition on placebo or ketamine. In Experiment 3, both ketamine users and poly-drug users showed me-pulse facilitation, similar to that observed in the high schizotypes. The ketamine group showed significantly less prepulse inhibition than the poly-drug controls.

8.9.1 Schizotypy

The key finding from the pilot study was of a difference in startle response to the 'me-pulse'. Whilst low schizotypes showed an inhibition of the startle response when they generated the startling stimulus themselves, the high schizotypes did not show such inhibition. In fact the high schizotypy group appeared to experience a facilitation of the startle response, i.e. their startle response was greater to self-generated pulses than to the unexpected pulse.

In relation to our aim of developing a new self-monitoring task, the results of this pilot study were encouraging. Supporting our initial predictions, there were differences on the me-pulse trials between high and low schizotypes but no differences on the pre-pulse trials. The low schizotypes showed an inhibition of the startle response following a me-pulse whereas the high schizotypy group did not. The inhibition by the low schizotypes on mepulse trials may reflect similar processes as those hypothesised to occur in self-tickling (Blakemore et al., 1999). These are that an accurate prediction is made of the sensory consequences of a self –produced action (in this case pressing the button to generate a startling noise) and this prediction results in an attenuation in response, as the startling stimulus is identified as self-generated. In the high schizotypes, it may be that a defective self-monitoring system results in an inappropriate, or absent prediction of the consequences of an action, which in turn means that no attenuation of the startle response occurs. This would be in line with theories of deficits in monitoring the output of information in schizophrenia (Frith, 1992) and is further supported to some degree by the correlations between decreasing mepulse inhibition and higher scores on some sub-types of schizotypal symptoms.

One problem for our new paradigm however, was that in low schizotypes the reduction in the startle response on me-pulse trials did not exceed the reduction observed on prepulse trials. Theoretically, as with tickling stimuli, a sensation that is self-produced would be subject to more inhibition than one which is simply predictable as it is subject to an efference copy (Frith et al., 2001). However, in this study there was no way of saying that the me-pulse was not just behaving as a pre-pulse in the low schizotypy group. It may be that as the startling stimulus was not generated by the subject

themselves as would be a scream, for example, then the application of the efference copy explanation is not as appropriate here. In addition, in the tickling study, the participant made a movement and then the same shaped movement was made by a robot hand on their hand. In the current study the participant pressed a button which resulted in a loud noise, it could be that the cross-modal, second-order nature of the action and response reduced the degree of influence of self-monitoring. Furthermore, as prepulse inhibition is itself a special phenomenon in the manner in that it inhibits the startle response, perhaps it was not appropriate to use this as the predictable stimulus. In future it may be helpful to investigate the effect of varying the degree of discrepancy temporally between pressing the button and the startle response, as theoretically if the me-pulse is using an efference copy to reduce responses, then with greater discrepancy low schizotypes should show responses more similar to the high schizotypes.

Another finding that was contrary to our initial predictions (that startle inhibition would be reduced or abolished in the high schizotypy group by the mepulse) was that there was some *facilitation* of the startle response compared to the pulse alone. As these are pilot data from a novel task the findings should be viewed with caution. As far as we are aware, no previous study has examined the response to self-generated startling stimuli, thus there is no existing literature to suggest what the mechanism behind this facilitation in high schizotypes may be. A literature exists that describes prepulse facilitation, where responses to startling stimuli are enhanced at long stimulus durations (usually < 2000ms). This is thought to reflect a classic activating effect (Graham, 1975) where the prepulse causes the subject to orient to incoming information. Facilitation has been found to be greater for attended to than unattended to prepulses (Schnell et al., 2000; Wynn et al., 2004; Hazlett et al., 1998) and simple attentional facilitation of the blink startle response has also been found previously in healthy volunteers even at short lead intervals (Neumann, 2004). Possibly these findings have some relevance here and suggest an interaction between attention and self-monitoring. As the green screen pre-pulse requires an action to be generated, it may be that in the absence of an intact self-monitoring system, the me-pulse simply causes greater attention to be allocated to the self-generated pulse than to the unexpected pulse that is passively attended to. This

explanation is not completely satisfactory as the prepulse should cause the subject to orient towards the startling stimulus as well and thus cause a similar facilitation of the startle response, although perhaps to a lesser degree. Another explanation might be that due to an abnormal central self-monitoring system, the prediction made of the sensory consequences of the action is even more discrepant with the actual consequences than if no prediction were made, resulting in a greater startle response. However these explanations are purely speculative. Further investigation could vary the intensity or nature of the startling sound to investigate the 'prediction' hypothesis. Examining mepulse inhibition under conditions of divided attention could examine the influences of attentional processes.

Prepulse inhibition in the high schizotypes was not different from the low schizotypes. Although many passive attention studies have failed to find PPI deficits in schizotypy, our findings are contrary to those of Schnell et al. (1995) who used a similar active attention paradigm to the current study and found impaired prepulse inhibition in high schizotypes. However, the latter study used an interval of 120msec whereas our lead interval was 420 msec, which is towards the end of the temporal range that elicits PPI. PPI is not thought to be as robust at longer lead intervals than 120mesc (Braff et al., 2001), so this could account for these findings. It has been suggested that PPI deficits observed in schizophrenia are related to attentional deficits associated with this disorder (Dawson et al., 1993). However, whilst we did not examine attention in this study, deficits have been found in high schizotypes (Braunstein-Bercovitz, 2000). PPI deficits are often not found in high schizotypy scorers (e.g. Abel et al., 2004) and were not found in this study. This may suggest something more complicated than simple attentional modulation of the startle response is occurring in individuals high in schizotypy. It may be that the PPI deficits observed in schizophrenia on similar paradigms are an artefact of medication or hospitalisation effects. Interestingly in a recent study using a passive attention paradigm in healthy volunteers, PPI at a very short lead interval (120msec) was increased with the use of monetary rewards (Hawk et al., 2004). This also implies a role for motivation in PPI which may also be a factor differing between schizophrenics and high schizotypy scorers.

8.8.2 Acute ketamine

Experiment 2 generated two main findings: firstly 'mepulse' inhibition observed with placebo tended to be reduced after an acute dose of ketamine; secondly, there was no difference in PPI between ketamine and placebo on this active attention paradigm.
The mepulse inhibition observed on placebo in Experiment 2 was consistent with the findings in low schizotypes in Experiment 1, demonstrating that this paradigm produces robust inhibition for self-generated startle in healthy subjects. Again the MePI was no greater than PPI, inferring no extra level of inhibition for self-generated startle compared to predictable startle. The potential explanations of this finding have been discussed above.

Unlike the high schizotypes, there was no facilitation of the startle response following the mepulse in the ketamine group. This was in line with our original speculation, and may imply that the normal self-monitoring is disrupted by ketamine. In relation to the finding of facilitation in high schizotypes then, this may represent either a more superficial or possibly more profound impairment to the self-monitoring system. Only one dose of ketamine was used in experiment 2, however it would be interesting to see if facilitation occurs following higher and lower doses of the drug.

The absence of PPI deficits following an acute dose of ketamine is consistent with some previous studies (Van Berckel et al. 2001, Duncan et al 2000). It is however difficult to compare the findings from this study as other studies used different doses and have not used target-controlled infusions. In addition, the lead interval in this study was much longer than that used in previous work and further, an active attention paradigm was used. As acute ketamine does not impair focussed attention (Chapter 2; Morgan et al., 2004a) then perhaps it is not suprising that ketamine did not produce a

deficit in active attention PPI. Ketamine did not produce any changes in habituation, latency or startle unlike some (Abel et al., 2004) but not all other (Duncan et al., 2001; Van Berckel et al., 1998) studies.

The finding of preserved PPI also differs from the preclinical literature where impairments in PPI following NMDA –antagonists are consistently found (e.g. Geyer et al., 2001). However in animal studies doses of ketamine are often 10 times greater than those administered in human research. As discussed by Grunze et al. (1996) there is NMDA dependent modulation of inhibitory intrinsic circuits in the CA1 region of the hippocampus. The sensitivity of these circuits may result in either an increase or decrease in hippocampal output. Feedback loops engaging the striatum and the thalamus are thought to protect the cerebral cortex from sensory overload (Carlsson et al., 1999). Glutamatergic synapses within these feedback loops have been shown to be important in PPI in animals (Swerdlow et al., 2001). Carlsson et al. also suggested a role for glutamate as a 'brake' or 'accelerator' of monoaminergic systems resulting in increased or decreased flow of information to the cortex. A dose dependent investigation of the effects of ketamine on PPI would be helpful to clarify whether an inverted U-shaped relationship between ketamine adminstration and PPI exists.

8.8.3 Chronic ketamine

The main findings from Experiment 3, comparing ketamine users and poly-drug users, were of reduced PPI in the ketamine group compared to the poly-drug users and of a facilitated mepulse startle in both groups.

To our knowledge this is the first study that has examined active attention PPI in ketamine users. The findings of reduced PPI are of relevance to the ketamine model of schizophrenia, given that reduced PPI is consistently found in this disorder. Again, as this paradigm used longer lead intervals than generally used in normal PPI these findings must be interpreted with caution, although PPI deficits have been found in schizophrenia patients at these lead intervals (Bolino et al., 1994). Our results are contrary to those described in the animal literature. Repeated administration of

ketamine has not been examined, although 14 days of treatment with PCP has been found to produce no long lasting changes in PPI in rats, despite evidence of significant neurotoxicity (Martinez et al., 1999). The relevance of findings from the animal studies is very limited by the active attention, instructed condition in which PPI occurred in this study. Animal paradigms are clearly uninstructed, passive attentional and as such are thought to rely on automatic processes. It has been suggested that the mechanisms regulating 'attentional' versus automatic (uninstructed') PPI differ substantially (Braff et al., 2001). Primarily, 'attentional' PPI is mediated by attentional mechanisms although other mechanisms are clearly involved, as was demonstrated by the preserved PPI in high schizotypes despite reports of impaired attention. Indeed, attention deficits in ketamine users who had ceased or reduced their ketamine use substantially were found in Chapter 5 of this thesis but have not been found in other studies (Curran & Morgan, 2000; Curran & Monaghan, 2001). Therefore it is unclear whether the PPI deficits are related to attention impairments, motivational problems or actual deficits in gating of sensory information.

If the finding of impaired PPI does pertain to actual gating deficits, the notion of glutamate as a 'brake' or 'accelerator' as discussed above may be relevant. Whilst no research has examined the effect of repeated ketamine use on glutamate transmission in humans, in animals chronic PCP administration produces disrupted glutamatergic activity (Lindahl & Keifer, 2004). A decrease in glutamate could act as an 'accelerator' to monoaminergeric systems (via the inhibitory cortico-striatal-thalamic loop) thus increasing information flow to the cortex, which could result in decreased prepulse inhibition. In addition, when compared with the two other experiments reported in this chapter, elevated levels of PPI were shown in the poly-drug using controls in Experiment 3. Increased PPI has been found in MDMA users compared to cannabis users and non-drug users (Quednow et al., 2004). The poly-drug users in this study were recreational MDMA users which may explain their elevated PPI. The apparently reduced PPI in ketamine users might be a function of elevated levels of PPI in poly-drug controls. However, ketamine users were matched with poly-drug controls on MDMA use, so theoretically should have experienced the same elevation in PPI. In

addition, although statistical comparison cannot be made due to different conditions, inspection of the results suggests PPI in ketamine users was lower than that observed following placebo administration or in low schizotypes.

Both groups showed facilitation of their startle response for self-generated noises similar to that observed in the high schizotypes. The possible reasons for this have been discussed above. Again this may reflect a self-monitoring impairment. Self-monitoring has not been examined previously in drug users however behavioural inhibition has been extensively investigated. Whilst in chapter 7 we did not find response inhibition impairments in ketamine users and poly-drug users compared to non-drug users on a simple Go-No/Go task, response inhibition impairments have been found previously in recreational drug users (M.Morgan, 1998). Response inhibition may likely reflect self-monitoring. An impaired ability to modulate and regulate one's own behaviour has been suggested to be one of the key deficits in drug dependence (Goldstein & Volkow, 2002) and self-monitoring must play some role within this. Drug users, even of drugs that do not induce physical dependence, often report feeling compelled to use the drug and describe their drug use as almost beyond conscious control. This is somewhat reminiscent of delusions of control, however instead of misattributing the locus of control to external forces, drug users attribute it to the power of drug. It may be that there is also an abnormal prediction system at work in drug users that means they are less able to identify their actions as their own. Entirely speculatively, a deficit in predicting the actual sensory consequences of their actions in drug users might also be a factor in why, even when the effects of a drug become aversive, drug users continue to abuse them.

In addition, these two groups scored highly on baseline levels of schizotypy, so these deficits may be unrelated to drug use and reflect the higher levels of schizotypy, which have been noted in the past in drug users (Nunn et al., 2001). However covarying for schizotypal symptoms did not alter the outcome of the analysis. Unfortunately a comprehensive analysis of schizotypy using a measure such as the O-LIFE was not conducted, so the median split was only on the basis of the schizotypal

symptomatology questionnaire. Correlations however demonstrated a relationship between dissociative symptoms and MePI deficits, indicating increasing dissociative symptoms with decreasing MePI. We could tentatively infer from this that dissociative sensations (e.g. feeling detached from their bodies) stem from a defect in self-monitoring.

If the mepulse is taken as an indicator of self-monitoring then it appears that ketamine users have deficits both in monitoring sensory output and gating sensory input. This pattern is most like that observed in schizophrenia, although a more thorough exploration of the actual symptoms exhibited by these users is warranted.

8.8.4 Methodological considerations

All of the studies employed relatively small numbers of participants and require replicating with greater numbers. The studies seemed of sufficient power to detect differences however the possibility remains that with greater numbers further differences could emerge. In addition, the samples used are comparable with other PPI research (for a review see Braff et al., 2001). We did not control for smoking in the schizotypy group or the drug using groups and smoking has been shown to affect PPI (Della Casa et al., 1998). However when smoking was added as a covariate into the analyses it did not affect the results. Furthermore, in the schizotypy study there was a trend for a higher level of startle in the low schizotypy group. The mechanism behind this is not clear. However this could be problematic in that it is not clear whether startle magnitude affects PPI - and thus potentially MePI - although evidence suggests that they are not consistently related (Braff et al., 2001) as long as neither are at ceiling or floor levels.

The chronic ketamine study was subject to the same limitations of other recreational drug user studies which have been discussed in previous chapters. However a benefit of this study was the use of urine screens to verify that participants were not under the influence of drugs at the time of testing.

Across all studies, there was some lack of consistency in the measures used to verify schizophrenic-like symptoms. As mentioned previously, use of the O-LIFE in all studies may have been helpful to correlate trait schizotypy with the current findings. In addition, as self-monitoring deficits are purported to relate specifically to positive symptoms, a thorough exploration of these in the acute and chronic ketamine studies would have been helpful to examine the relationship between these and self-monitoring deficits.

In relation to the task, further validation is required before we can say that the pattern obtained is due to self-monitoring deficits and not another mechanism. Ways this may be achieved were outlined above, including manipulating the delay and nature of the stimulus and dividing attention. Another way of shedding light on this would be by examining evoked related potentials (ERPs) to self and computer generated stimuli. A dampening of the N1 potential has been found previously when speaking in an ERP study (Ford et al., 2001) and a magnetoencephalographic (MEG) study (Curio et al., 2000). To see if such a dampening occurs with self-generated startle might clarify whether the proposed self-monitoring mechanisms i.e. forward models are inducing an attenuation of the startle response or whether the attenuation observed in the low schizotypes and on placebo is in fact simply a result of the mepulse acting as a prepulse.

Despite the problems with the task it is clear that something unique is occurring in the high schizotypes and drug users to produce a greater response when the startling stimulus is generated themselves. The findings of these pilot studies suggest that the monitoring of actions i.e.'output' may be impaired in high schizotypes, in drug users and following an acute dose of ketamine. For ketamine users, the PPI deficits suggest that repeated ketamine use may also affect the gating of incoming sensory information i.e. 'input'. The similarity between the pattern of effects observed on the mepulse in high schizotypes and drug users is interesting and may relate to recent theories that similar underlying processes are impaired in both schizophrenia and drug abuse (Chambers et al., 2001). Further understanding the suggested impairment in self-

monitoring processes may aid in treatment for these disorders. In response to the question we originally posed "Can one startle oneself?", it would appear that in healthy volunteers with no indication of psychosis proneness the answer is no. However healthy volunteers who experience high levels of schizophrenic-like symptoms can not only startle themselves but in fact startle themselves more than does an unexpected stimulus, as can poly-drug users and, to a much lesser extent, volunteers who have received a single dose of ketamine.

Chapter 9: General Discussion

"Facts never speak for themselves but are at the mercy of their interpreters..."

Franz Kafka

9.1 Overview

This thesis set out to examine some of the effects of acute administration and chronic self-administration of ketamine. Studies investigated the effects of ketamine on memory systems, including reward related processes, and the subjective effects of the drug, including dissociative and schizophrenic-like symptoms. The degree to which this thesis has further characterised the acute effects of ketamine will be summarised first in this final chapter. Then the clinical implications of the data presented in this work will be considered in light of two main research questions:

1. What are the consequences of ketamine abuse, its abuse potential and the factors that may underlie its continued use?
2. What are the implications of the findings of this thesis for the acute and chronic ketamine models of schizophrenia?

After the summary and the above questions have been considered, I will briefly discuss some of the general conceptual limitations constraining the work in this thesis and the methodological issues that arose. Finally I will reflect upon some of the potential implications of this work for future research.

9.2 Acute Effects of Ketamine on Cognition

9.2.1 Episodic memory

The work of this thesis replicated the impairment in verbal memory observed in earlier studies (e.g. Krystal et al., 1994; Newcomer et al., 1999; Adler et al., 1998), extended these findings by examining the effects of an acute dose of ketamine on both recall and recognition and used levels of processing and source memory tasks to tease apart the relative effects on different components of episodic memory. The impairment observed on source memory was similar to that reported in a recent paper (Honey et al., submitted) and demonstrates the capacity of ketamine to impair information for contextual details at encoding along with more general mnemonic impairments. Whilst the binding of contextual details to memories is impaired by ketamine, as was evident by the source memory deficits, performance on this task was found even on high dose ketamine to be well above chance (unlike recognition memory in other previous studies e.g. Malhotra et al., 1997). This suggests that the elaborative encoding condition used in this task was beneficial to subjects following an acute dose of ketamine. Therefore it may also be that ketamine also blocks the umprompted initiation of mnemonic strategies that will later facilitate accurate performance on a source memory task, for example using a deeper level of processing at encoding.

Ketamine was found to impair recall of information learnt after drug administration but not before. This supports the notion, which has been suggested by previous research (Malhotra et al., 1996; Hetem et al., 2000; Honey et al., submitted), that ketamine impairs encoding but not retrieval of information learnt on the drug. However, it is possible that the behavioural tasks used in this thesis were not sensitive enough to detect ketamine induced retrieval deficits. Despite the absence of behavioural effects on retrieval processes observed in this work, recent neuroimaging research has demonstrated a reduced left prefrontal activation when retrieving information encoded prior to ketamine infusion (Honey et al., submitted). This is thought to represent an inability to access the contextual details associated with a remembered stimulus. The

use of compensatory strategies in retrieval therefore remains a possibility and should be further investigated. There have been previous suggestions that ketamine affects consolidation processes into long term memory (e.g. Krystal et al., 1994). However in this thesis, unlike the latter study, delayed recall was not affected disproportionately to immediate recall, and the pattern of performance mimicked that observed in healthy subjects, but simply at a lower level overall. In addition, when given soon after encoding, ketamine did not reduce the amount of information retrieved on drug as one might perhaps expect if consolidation was impaired.

The episodic memory data collected in this body of work confirm the role of the NMDA-R in the synaptic plasticity underpinning learning and memory in humans. Although the picture may be more complex than a simple blocking of LTP. Theoretically, generalising from activity at a cellular level, this disruption of episodic memory may more plausibly reflect the greater affinity of NMDA-R antagonists for blocking inhibitory rather than excitatory activity (Grunze et al., 1996). Administration of ketamine is thought to preferentially disrupt feedback inhibition on interneurons (Grunze et al., 1996). This disinhibition produces a loss of adaptive functional modulation, or "tuning" of glutamatergic activity (Krystal et al., 1999) in the cortex. The inappropriate recruitment of neurons, temporally or spatially, causes a disproportionate magnitude of activation (Grunze et al., 2000; Lisman et al., 1998) and a resultant reduced capacity to terminate a response or process the next input. This may cause a loss of regionally specific functions for example "stimulus binding" in the hippocampus and working memory in PFC (Krystal et al., 1999), which may in turn produce these observed memory impairments.

9.2.2 Semantic Memory

Semantic memory was an important topic of investigation for this thesis as there have been suggestions that ketamine is one of the few drugs to affect this memory system (Curran & Weingartner, 2002) and there was no clear evidence with regards to the existence of semantic memory deficits following ketamine administration. In our initial study (Chapter 2), a smaller number of sentences were verified on ketamine in the

speed of comprehension task which indicated some semantic processing impairment. However, verbal and category fluency were shown to be unaffected by ketamine (Chapter 6), in line with some previous studies (Newcomer et al., 1999; Krystal et al., 1999). Due to the equivocal nature of these results a further study (Chapter 4) examined semantic processing more specifically using a semantic priming paradigm. Following an acute dose of ketamine, we found *inverse* priming at a long SOA but not at a short SOA. This was a highly novel finding, as inverse priming has only been found before in studies of emotional priming (Rossell & Nobre, 2004). The preservation of priming at a short SOA suggested that automatic spreading of activation in the semantic network is unimpaired. Controlled processing, on the other hand, may be disrupted as is evident from the inverse priming at a long SOA.

Based on the three processes proposed to be involved in semantic priming (see Chapter 4): automatic spreading of activation, expectancy and semantic matching, we interpreted this as a possible ketamine-induced impairment of semantic matching, a post-lexical process that matches targets and primes for semantic similarity. This may pertain to the notion of the NMDA-R involvement in contextual processing or 'cognitive co-ordination' (Philips and Silverstein, 2003). However additionally, some of the 'inverse priming' observed was due to facilitation in processing of unrelated targets at a long SOA. Theoretically, this could reflect the dysregulation of inhibition that has been suggested by neural network models following NMDA-R antagonist administration (Grunze et al., 1996). Whilst it is accepted that it may be overly reductionist to presuppose that failure of inhibition at the cellular level mediates failure of inhibition at the cognitive level, there is evidence from neural network modelling to suggest that this may be the case (McCarley et al., 2005). A key element of both cognitive and biological networks is the ability to control excitation and maintain stability. In a semantic network, activation of a concept or representation is thought to produce various levels of excitatory buildup, which is reflected in competition between simultaneously activated representations (Nestor et al., 1998). The dysregulated network inhibition could, at this longer time period produce this facilitation of

responding to normally distal concepts in a network, which may be behaviourally observed in facilitation of processing of unrelated words at a long SOA.

9.2.3 Working Memory, Attention and Executive functioning

Attention on the 0-back component of the N-back task was unimpaired by an acute dose of ketamine. This replicates the findings of other studies (e.g. Adler et al., 1998; Newcomer et al., 1999) and is clearly important as attention is involved in the 1-back and 2-back (as well as every cognitive task). Working memory was found to be impaired acutely by ketamine on both the 1 and 2 back section of the N-Back task. However, ketamine did not disproportionately affect the ability to hold on line the two previous letters, compared to one previous letter. This may indicate that maintenance in working memory is unaffected by ketamine but that updating of information is impaired and this supports other observed ketamine deficits in backwards digit span (e.g. Honey et al., 2003).

With regards to executive functioning, trailmaking was unaffected overall by acute ketamine administration, although there was some evidence of slower performance on part B of the task. Successful performance on the trailmaking task requires maintenance of a sequence in working memory (parts 1 and 2) and cognitive flexibility (part 2). As performance on part 1 of the task is intact then this may be further evidence that maintenance of information may be preserved after ketamine. The slowing on part 2, where participants are required to switch between two tasks, may indicate that cognitive flexibility is impaired by the drug.

Ketamine did not affect verbal fluency, which taps retrieval, selection and monitoring processes. Response inhibition / suppression was assessed using the Hayling task and the Go/No-go task. On the Hayling task participants made more errors on Part B of the task but not part A. This was indicative of disrupted response inhibition but not response initiation. However, on a more simplistic measure of response inhibition, the Go/No-go task, participants on an acute dose of ketamine made less correct responses but showed no difference in the number of response inhibition errors suggested that

inhibiting simple prepotent responding was intact following acute ketamine on the Go/No-go. The reduced number of hits may indicate that the ketamine group are 'over-inhibiting' which may perhaps reflect a compensatory strategy to counteract their perceived impairment. Therefore a more parsimonious explanation of the findings of the Hayling task, rather than impaired response inhibition, may be that ketamine-related strategic or semantic impairment renders subjects unable to generate contextually irrelevant alternatives. Overall then from these executive functioning and working memory data, acute ketamine may have induced a deficit in cognitive flexibility but left selection and monitoring processes intact. A problem for the role of the proposed role of the NMDA-R theoretically in 'cognitive co-ordination' is the similarities shared between this notion conceptually and that of executive functioning, thus the relatively preserved executive functioning we observed following acute ketamine may provide evidence against this theory. However, the suggestion of this work is that deficits in executive functioning following acute ketamine administration stem from problems in the integration and manipulation of information, which, intuitively at least, would seem to be the most prototypical 'co-ordinating' function.

9.2.4 Perceptual priming and Procedural learning

Perceptual priming was preserved following a single dose of ketamine and procedural learning was impaired, although this may have been complicated by slower reaction times in the high dose ketamine group as previously discussed. This distinction is interesting as in a variety of disorders (e.g. amnesia, schizophrenia) it is explicit processes that are predominantly impaired and implicit processes that are preserved, however following ketamine two implicit processes are differentially effected. It may be that this procedural deficit is mediated by reduced DA-ergic transmission in the basal ganglia, as is observed in Huntington's disease. A further possibility may be that as procedural learning required the encoding of contextual relations between a set of stimuli, in order to learn the sequence appropriately, unlike priming which requires the simple encoding of stimulus features, then it was this process that was impaired. It may be that the distinction between contextual / non-contextual memory may be more relevant to the findings of this thesis than the implicit/ explicit distinction. The latter

may also relate to the findings of other tasks such as the 0-back and the Go/No-go task, where performance was relatively unimpaired. Neither of these tasks required the encoding of contextual relationships between stimuli for correct performance. These findings contrast with those of previous work on tasks such as the AX-CPT task, where response inhibition / sustained attention errors following ketamine have been found but only on B-X trials (Umbricht et al., 2001; see Chapter 1) i.e. those that require the formation of a trace of transient contextual relations between stimuli. As the Go/No-go and 0-back tasks required responding or non-responding only to a specific stimulus, i.e. monitoring and not integration of information, this may explain why performance on these simple tasks was relatively preserved.

9.3 What are the consequences of ketamine abuse, its abuse potential and the factors that main underlie its continued use?

"*I can't understand why anyone would want to take the stuff. It gives you nightmares doesn't it*?" Consultant Psychiatrist in Addictions, quoted in Jansen, 2001.

Given the burgeoning population of ketamine users, two of the central questions of this thesis were i) what happens to people when they repeatedly use ketamine and ii) what is the abuse potential of the drug? Hence we conducted the first studies to investigate the impact of repeated ketamine self-administration in humans. Initially, by finding no memory or attentional impairments 3 days after an acute dose of ketamine in healthy volunteers (Chapter 6), we confirmed that any day 3 effects were likely to be chronic effects of the drug and not simply residual effects. We then concentrated on a characterisation of some of the cognitive effects of ketamine abuse and briefly attempted to examine some of the reward related processes involved in its maintenance.

9.3.1 Episodic Memory

Prose recall was found to be impaired in ketamine users 3 days after drug use (Chapter 5). In addition, item recognition and source memory were disrupted on the night of

drug use, however 3 days later in ketamine users only source memory was found to be impaired, in the presence of intact item recognition. The day 3, or 'chronic' data may be explained using a familiarity versus recollection distinction (see Chapter 1). Ketamine use may have impaired recollection in the face of relatively preserved familiarity. This is in evident by the impaired prose recall and source discrimination observed, in the presence of relatively intact item recognition.

The episodic memory impairment observed on the night of drug use in ketamine users tested in phase one of the follow-up study reported in Chapter 5 was comparable to that observed following an acute dose of ketamine in healthy volunteers. However, given that doses reported by ketamine users were much higher than those administered in the acute studies, we may infer that these users have developed some degree of tolerance to the memory impairing effects of ketamine, and/or may have exhibited pre-existing differences in memory functioning. Tolerance to the memory impairing effects of ketamine might theoretically be related to NMDA-R upregulation, which has been observed in animal models following repeated NMDA-R antagonist administration (Arvanov & Wang, 1998).

9.3.2 Semantic Memory

The pattern of semantic memory impairments in ketamine users differs from those seen following an acute dose of ketamine, in that overall they appear to be more profound. On the speed of comprehension task ketamine users completed less sentences and made more errors than poly-drug controls, which is indicative of gross semantic impairments, as errors on this task are relatively difficult to elicit (Rossell et al., 2001). Ketamine users also generated fewer exemplars in category but not verbal fluency. As discussed in Chapter 5, the dissociation of performance on the above tasks may indicate impaired storage of rather than access to semantic knowledge (Allen et al., 1993). This assertion is also supported by work reported in Chapter 4, from the semantic priming study. Semantic priming was again found to be reduced for the long SOA, indicating an impairment in controlled semantic processes as discussed above. In addition however, priming was lower for low frequency words. This suggests that some degradation of the

semantic store may have occurred in this population. Alternatively, general semantic retrieval processes may be impaired following chronic ketamine use. This would be conistent with impaired category fluency and the preserved priming at a short SOA.

9.3.3 Working Memory, Attention and Executive Functioning

In chronic ketamine users, an impairment to attention was evident by slower performance on the digit cancellation task. The absence of errors on this task suggests that simple vigilance may be preserved in ketamine users but that monitoring of information was simply more effortful for these individuals. There was no correlation between attention and impaired performance on other tasks, such as prose recall, therefore attentional deficits were likely not underlying other cognitive impairments.

In the ketamine users, working memory was investigated using the serial seven's task. Whilst in the original study upon which the follow-up longitudinal study (Chapter 5) was based, performance on the serial seven's was impaired on the night of drug use (i.e. acute on chronic effect: Curran & Morgan, 2000), no impairment was evident 3 days after drug use. However, findings from this task may be influenced by baseline numeracy abilities (which may in turn be influenced by baseline working memory). Performance on the verbal fluency task was intact, however there was a trend for more perseverative errors in ketamine users. On the Go/No-go task when drug-free there were no differences between ketamine users and poly-drug controls (i.e. chronic effects), however on the night of drug use ketamine users made more false alarms and less hits. This evidence is inconclusive with regards to response inhibition; the false alarm increase could signal response inhibition deficits, however combined with less hits these data may indicate globally inaccurate performance. This contrasts with the animal literature where chronic NMDA-antagonism is associated with response inhibition and working memory deficits (see Jentsch & Roth, 1999 for a review).

It seems somewhat paradoxical that the changes following repeated antagonism of the NMDA-R may result in a similar, if not slightly more selective, profile of effects on cognitive functioning as acute antagonism. However neural network models suggest

that theoretically both hypoglutamatergic states (reduced glutamatergic signal and associated excessive inhibition) and hyperglutamatergic states (heightened activation or inhibitory deficits) could produce similar cognitive disruptions (Lisman et al., 1998; Grossberg, 1984). In addition, abnormal hippocampal neurogenesis has been observed in rats following repeated ketamine, along with a reduced sensitivity of GABA-ergic interneurons (Keilhoff et al., 2004) which again could theoretically produce disruptions in information processing similar to those described following acute ketamine. In addition, a reduction in DA transmission in the prefrontal cortex of monkeys has been observed following repeated NMDA-R antagonism. However the cognitive impairments observed following repeated ketamine self-administration in this thesis are less indicative of a DA-ergic mechanism, as in general DA-ergic impairments produce more wide ranging deficits on executive functioning and working memory tasks (Paulus et al., 2002) than were observed in our, admittedly limited, investigation.

9.3.4 Schizophrenia-like and dissociative symptoms.

There was some evidence of ketamine users having elevated levels of delusions and persisting subjective effects of ketamine, whilst drug free. Both ketamine users and poly-drug controls scored more highly on schizophrenic-like symptoms scales than placebo controls and in some studies scored in the range of healthy participants on ketamine. Of note in consideration of the persisting schizophrenia-like effects are the difference results obtained in studies throughout this thesis. In Chapters 5 and 7 ketamine users showed evidence of some schizophrenic-like or dissociative symptoms when drug free, however in Chapters 3, 4 and 8, no such persisting effects were apparent. A wide variety of factors could theoretically account for these differences, most notably participants' different degrees of ketamine use. However additionally, other factors such as age of first use, which were not explored in this thesis could also play a role in differential symptoms. There is a growing body of preclinical evidence that suggests that the age at which NMDA-R hypofunction is installed can lead to very different clinical and neuropathological representations (Olney & Farber, 1999; Olney et al., 1997; Farber et al., 1998; Newcomer et al., 2000).

9.3.5 Reversibility of impairments

Three years later, after reducing use of ketamine considerably, some semantic memory recovery was evident (Chapter 5). The semantic processing improvement was correlated with reduction in ketamine use. It is not yet clear what the mechanism of this reversible semantic impairment may be. It could be a compensatory psychological mechanism, that has been adopted to deal with the semantic impairments experienced by ketamine users or it could be reversible neurotoxicity similar to that observed in rats (Olney et al., 1989).

However, persisting episodic and attentional impairments were still evident in ketamine users when compared to poly-drug controls after reducing their use of the drug nearly completely. This may relate to the irreversible cell death observed following repeated high doses of high affinity NMDA-R antagonists (Olmey et al., 1991). At this time the exact mechanism remains unclear. Regardless, these persistent memory and attentional impairments have worrying implications for ketamine abusers.

9.3.6 Abuse potential

The question of factors underlying and maintaining ketamine use is a more complex one and any inferences from this thesis should be viewed as purely speculative. As outlined in previous chapters, ketamine is self-administered in rats and non-human primates (Winger, Palmer, and Woods, 1989; Marquis, Webb, and Moreton, 1989) and in rats, produces conditioned place preference (Layer , Kaddis, and Wallace, 1993). However, the strong psychedelic effects of ketamine are such that approximately 65% of regular drug users who try it, do so only once (IDMU, 2005). However for a subset of users, such as those studied in this thesis, the rewarding effects are such that they wish to take the drug regularly and in some cases daily.

In previous chapters we have considered the abuse capacity of ketamine in terms of the 'I-RISA' model of drug abuse (Goldstein & Volkow, 2001) which has subsequently been updated (Volkow et al., 2003), but as discussed in Chapter 7, this theory may be more appropriate to drug dependent individuals. We found no clear evidence of response inhibition impairments following acute or chronic ketamine, and additionally none in a recreational drug using control group. Therefore to better answer our question as to why ketamine users wish to take the drug we have incorporated the findings of this thesis in a framework of reward proposed by Berridge and Robinsion (2003) and discuss the I-RISA briefly later. Berridge & Robinson argue that reward should be separated into its specific psychological components which they suggest to be: 1) learning 2) affect or emotion and 3) motivation. These component processes are thought to be interactive and within each level both implicit and explicit processes operate.

In terms of learning, ketamine impairs explicit learning processes, (as is evident from the episodic memory deficits observed in this thesis), whilst leaving some implicit processes intact. Perceptual priming and habituation were preserved following ketamine in healthy volunteers, two different processes that could contribute to continued drug use. Highly speculatively, habituation may be viewed as a form of low-level conditioning, which is know to be involved in developing stimulus-reward associations between a drug. Priming may allow the encoding of the basic stimulus features which become associated with reward. An apparent paradox for understanding the neurotransmitter basis of ketamine abuse, is that the NMDA-R is proposed to be involved in synaptic plasticity that allows learning of associations important to drug abuse (Thomas & Malenka, 2003) and competitive NMDA-R antagonists have been used in treatment of heroin and cocaine addiction (e.g. Krupitsky et al., 2001). However, subtle differences that occur following repeated ketamine administration, which yet remain to be elucidated, may eventually explain this seeming contradiction.

Affective modulation is also thought to be involved in the maintenance of drug abuse. In an acute study in this thesis, healthy volunteers rated themselves subjectively as

'liking' the effects of ketamine at low doses however this liking became diminished at higher doses. This may relate to the proposed role of the NMDA-receptor in conveying an 'intoxication signal' in response to a large dose of ethanol (Krystal et al., 1999). In ketamine users however, at much higher reported doses of the drug, liking was greater than in the healthy volunteers. As these measures are based on subjective rating scales in different populations, it is not clear how comparable they are. However the increased subjective 'liking' of ketamine may imply either sensitisation to its pleasurable effects or pre-existing differences that blunt negative response to the drug. Sensitisation to the locomotor effects of NMDA-R is known to occur in animals (Xu & Domino, 1994; Phillips et al., 2001). Sensitisation may be linked with the implicit learning processes detailed above and may reflect of the activation of the mesolimbic DA pathways. However, in terms of 'liking', DA is thought to play less of a role than in salience and incentive processes detailed below (Berridge & Robinson, 2003).

Pre-existing differences in ketamine users that predispose them to use of the drug are another interesting possibility. Relevant to this, recent work has found that relatives of alcoholics have a blunted response to the dysphoric and yet heightened response to the euphoric effects of ketamine (Petrakis et al., 2004). This is certainly a candidate mechanism in differences in the liking responses reported in healthy volunteers and ketamine users. Altered baseline NMDA-R function could lead to the effects of the drug being perceived as more positive. Related to the liking ratings mentioned above, in the acute ketamine studies volunteers self rated contentedness was higher in the low dose ketamine group than the high dose group. However, ketamine users' ratings of contentedness did not differ on drug when compared with drug free poly-drug control users. Thus ketamine users do not seem to be taking the drug for explicit pleasure, it may be that their rated 'liking' of the drug relates to implicit hedonic processes.

The third process proposed to be involved in drug mediated reward is motivation. Under this term, Berridge and Robinson include implicit incentive salience processes as well as conscious desire for a drug. Both of these processes were tested to some extent in this thesis. Incentive salience was examined to in the novel Drug Go/No-go task.

Problems with this task have been discussed in Chapter 7. However, taking these into account, there was some suggestion from this study that ketamine users and poly-drug users may both have a reduced attentional bias for naturally reinforcing stimuli compared to non-drug users. If this is replicated, a DA-ergic mechanism is likely to be responsible as there were no ketamine specific differences. Hypereponsivity of the DAergic modulation of the nucleus accumbens has been demonstrated to be a consequence of long-term PCP exposure (Jenstch et al., 1998) and could contribute to the incentive salience processes which are a clear component of drug abuse.

Conscious desire for the drug was examined with subjective scales of 'wanting'. Healthy volunteers on a low dose of ketamine wanted the drug more than those on a high dose, and both groups 'wanted' the drug more than placebo. In users, the wanting of the drug was greater than in healthy volunteers, which may again indicate sensitisation to its motivational properties. Again, however, caution should be exercised when making these comparisons across populations on a subjective effects scale.

Apart from the reward based processes discussed above, there are other factors that may play a role in maintaining ketamine abuse. The drug has a short duration of action, which has been demonstrated to be involved in the abuse potential of a drug (Feldman et al., 1996) and additionally in the bingeing behaviour that occurs on ketamine (Jansen, 2001). From a sociological perspective, the majority of ketamine users are young, white, middle-class males. For the studies included in this thesis, most of the participants were recruited from 'squat parties' or other underground dance venues. The sub-culture to which these users belong expresses dissatisfaction with conventional lifestyles. Anecdotally, from interviews with users, they report taking the drug because its effects are 'interesting', some users view it as an exploration of their own consciousness (Jansen, 2001). Thus even despite of perceived unpleasant effects people may continue using the drug as it as it relieves boredom, rather than providing any pleasurable effects *per se*. This may account for the dissociation between 'liking the drug' and conscious happiness ratings when on the drug.

It is worth noting that in the longitudinal study reported in Chapter 5, participants had reduced their ketamine use by 88.3%, with nearly half having not used the drug for 6 months. It would appear from this sample that the drug has a relatively low dependence forming potential. However, as noted in Chapter 5, it may be that participants who were heavier users and subject to greater downward social mobility were the participants we were not able to contact for follow-up.

9.4 What are the implications of the findings of this thesis for the ketamine model of psychosis?

Throughout the thesis reference has been made to the use of acute ketamine as a model of schizophrenia (e.g. Javitt & Zukin, 1997). In addition, I have cited studies that suggest that chronic administration of NMDA-antagonists may be a better model of aspects of schizophrenia, at least in animals (e.g. Jentsch & Roth, 1999). Following repeated ketamine administration in animals there are abnormalities in gene expression (Keilhoff et al., 2004) and changes in DA and Glu binding, possibly suggestive of schizophrenia-like changes (Bernstein et al., 2004). Although no attempt was made in this research to thoroughly test ketamine as a model by directly comparing its effects in healthy volunteers and ketamine users to schizophrenics on the same tasks, it does provide an opportunity to explore, to some extent, the degree to which chronic ketamine or acute ketamine in humans better 'models' the symptoms of schizophrenia.

One of the strengths of the acute ketamine model is its capacity to induce cognitive deficits which have been consistently associated with schizophrenia, unlike other pharmacological models. A problem for comparing ketamine's effects with the cognitive deficits of schizophrenia is that, while effects in schizophrenia are relatively consistent across studies, the magnitude of impairment may vary, as would be expected from such a heterogenous disorder (Green et al., 2000). In addition, tasks have been categorised as referring to different cognitive functions in different studies (Jaeger et al., 2003). Hence it is often difficult to gauge which, if any, is the preferential

impairment in schizophrenia. Further, cognitive deficits seem to be profound and wide-ranging and often confounded by medication effects and long hospitalisations. With these caveats in mind, the effects of ketamine will now be considered in light of evidence from patients with schizophrenia.

In terms of episodic memory impairments, acute ketamine induced both source and recognition memory impairments on a task that yielded only source memory impairments in drug-free ketamine users. The selective impairment of source memory is more congruent with the impairments reported in the schizophrenia literature (e.g. (Danion et al. , 1999; Brebion et al., 2002) . From our exploration of semantic memory, there was an indication of a deficit in storage of semantic information in chronic ketamine users, whereas following acute ketamine healthy volunteers appeared to have problems in accessing semantic knowledge. The former is more consistent with schizophrenia (e.g. Danion et al., 1999). Both groups, however, displayed an inverse priming pattern that has not been observed in schizophrenia before. Hence it is unclear to what extent the pattern in either group reflects schizophrenia-like impairments.

The working memory impairment observed on the N-Back task in the acute ketamine group is reminiscent of that observed in schizophrenia on the same task. However on this task schizophrenics make disproportionately more errors on the 2-back part of the task (Perlstein et al., 2001), which were not observed following acute ketamine and are suggestive of a maintenance (rather than manipulation) problem. The ketamine users were not impaired on a potentially more taxing working memory task, although this comparison is complicated by the use of different tasks across the two studies. Neither group were impaired on response inhibition, which indicates intact monitoring processes in executive functioning. Response inhibition deficits have consistently been observed in schizophrenia (e.g. Leeson et al., 2005), although these have frequently been tapped with more complex measures such as the Hayling task, which did demonstrate effects of acute ketamine (high dose) in this thesis. The lack of impairment to perceptual priming in both groups is consistent with the schizophrenia literature. An impairment in focussed attention was observed in ketamine users, as tested by the digit

cancellation task (although this also taps visual scanning and motor speed). No impairment on the 0-back was observed following acute ketamine. This is much less demanding however and impairments may have been evident on the digit cancellation test. In schizophrenia, impairments in attention have been observed, however not on the 0-back task. Other studies have demonstrated ketamine induced impairments on more demanding attentional tasks such as the AX-CPT (Umbricht et al., 2000).

In reference to the original question of whether an acute dose of ketamine or chronic self-administration provides a better model of the cognitive deficits in schizophrenia, unsurprisingly, the current results do not yield a simple 'yes' or 'no'. They suggest that in terms of semantic and episodic memory, cognitive deficits following repeated self-administration of ketamine may be more similar to those observed in schizophrenia than those observed following the acute doses of the drug used here. However, for working memory and aspects of executive functioning, acute ketamine may produce a more similar pattern of impairment. In schizophrenia, working memory deficits are thought to be the cognitive function least affected by atypical antipsychotic treatment (Harvey et al., 2003) therefore in this respect acute ketamine may prove a more useful model for investigation of novel pharmacotherapies. However some researchers have argued that episodic and semantic memory impairments in schizophrenia are more profoundly affected (Tamlyn et al., 1992) and, of the range of cognitive impairments, are the best candidate for a differential deficit (e.g. (Saykin et al., 1991). On this basis, chronic ketamine self-administration may be a better model.

Although in this thesis analyses of schizophrenia-like symptoms were not the primary focus of our work, evidence from the SSQ and ADSS is useful in consideration of the adequacy of the ketamine model. In terms of symptoms, acute ketamine does reliably induce schizophrenic symptoms. Exercising caution while we do so, comparing across the studies the higher doses of ketamine used in the laboratory often induced schizophrenic symptoms numerically equivalent or lower to those reported in the chronic ketamine users when not on the drug. However, the finding of elevated schizophrenic symptoms in ketamine users is a less consistent one as in some cases

similar symptoms were observed in the poly-drug control group which, as discussed previously, may reflect underlying trait schizotypy. By far the greatest schizophrenic-like symptoms are reported by the ketamine users when under the influence of the drug and this probably reflects the higher doses used. Delusional symptoms were found to be greater in ketamine users than polydrug controls in one study (Chapter 6), but not others (Chapter 4, Chapter 8) although the users in the latter studies reported taking lower doses of ketamine which may account for this.

Perhaps, theoretically, the absence of consistent schizophrenia-like effects in drug-free ketamine users does not detract from their potential validity as a model of aspects of schizophrenia. If, as is increasingly suggested by the schizophrenia literature, chronic NMDA-R antagonism does occur endogenously in this disorder (see Krystal et al., 2000 for a review), then repeated ketamine administration may mimic the functional and neurodegenerative consequences of such persistent antagonism. Although no work exists as yet to indicate whether NMDA-R upregulation occurs in ketamine users, it seems reasonable to conclude that this is the case from the animal literature (Keilhoff et al., 2004) and knowledge of the general effects of repeated drug administration (Feldman et al., 1997). There is also a literature to suggest this is the case in schizophrenia (e.g. Meador-Woodruff & Healy, 2000). Thus, whilst not mimicking the aetiology or acute phases of the disorder, the ketamine abusing population may depict later functional changes. Highly speculatively, the use of both chronic and acute models of schizophrenia may allow dissociation of the original glutamatergic-induced causes / symptoms and the subsequent consequences of chronic psychotic symptoms. Such dissociations were observed in this thesis. One example is the impaired PPI observed in ketamine users but not in volunteers following acute ketamine. If the latter conjecture is true this may suggest that PPI deficits are a result of neuroadaptive changes that occur as a result of repeated NMDA-R antagonism and not an initial cause of schizophrenic symptomatology. This idea is supported by the absence of a PPI deficit in psychosis prone subjects studied in Chapter 8 and the fact that PPI deficits in schizophrenia are seen only in chronic schizophrenics (Braff et al., 2001).

In our consideration of the schizophrenic-like properties of ketamine, we wished to look at whether certain processes that theoretically underlie symptoms of schizophrenia are also impaired after ketamine. An influential theory of the origins of positive symptoms in schizophrenia was that of Frith (1992). This has been discussed previously in this thesis (see Chapter 9). We examined self-monitoring, which has been suggested to be disrupted in schizophrenia, in two ways; looking at self-monitoring of actions using the Mepulse inhibition task and monitoring of goals using the Go/no-go task. The results of this thesis did not suggest that a self-monitoring deficit similar to that proposed by Frith occurs following ketamine. There was some evidence that MePI was abolished following ketamine on our novel task. However, there was no clear indication of a deficit in inhibiting pre-potent responding, on acute ketamine or in ketamine users on the Go/No-go task. As the MePI paradigm was a novel one, and one not as yet validated with schizophrenia patients, it is difficult to make inferences from the findings on this task. In terms of schizotypy however, both ketamine users and poly-drug controls were most similar to high schizotypes. This may have been confounded by higher trait schizotypy in drug users. For the high schizotypy group and both ketamine users and poly-drug controls there appeared to be some *facilitation* of startle when they generated the startling stimulus themselves. Hence Frith's theory does not seem applicable to these data. Theoretically, the MePI findings may be explained by a more expansive notion, still compatible with that of Frith (1992), that suggests that in schizophrenia there are abnormalities in the representation of the egocentric-allocentric world. This theory suggests that in certain cases of schizophrenia, internal or familiar information becomes facilitated and novel or unfamiliar information tends to be ignored (Cohen & Servan-Schreiber, 1993). Purely speculatively, it may be that on the Mepulse task, the response to self-generated startling stimuli was enhanced as internal information is overaccentuated in drug users and psychosis prone subjects.

9.5 Conceptual Issues

Several conceptual issues limited the interpretation of findings from this thesis. These have been briefly addressed previously but will be summarised here.

In terms of 'modelling' schizophrenia, the utility of any pharmacological probe is limited in several domains. The heterogeneity of the disorder and symptoms associated with it mean that it is unlikely that any single pharmacological agent will able to be adequately mimic every aspect of this complex disease. Furthermore when comparing across actual cognitive and behavioural symptoms elicited, the inconsistencies in the schizophrenia literature itself complicate analysis. In addition, post-mortem and neuroimaging data suggests that 'schizophrenia' involves a complex interplay between multiple neurotransmitter systems which in turn produces many neurodevelopmental and adaptive changes over time. It is highly unlikely that the acute, and to a lesser extent, chronic administration of a drug could adequately reproduce such a pattern of effects. Moreover abnormal brain morphology has been observed in schizophrenic patients which, particularly for the acute ketamine model, is unlikely to be elicited from a single dose of psychotomimetic drug. In addition, schizophrenia research has found regional selectivity of impairments which is unlikely to occur following administration of drug acting diffusely across the brain. Chronic ketamine may be more likely to model aspects of the disorder, given it may possibly produce some of the above structural and neuroadaptive changes. In future it may be more realistic and productive to focus on modelling specific symptoms rather than the 'whole disorder'.

A further conceptual problem for relating the cognitve effects observed in this thesis to particular receptor (e.g. the NMDA-R) functioning is the diffuse action of the drug and its downstream effects on other neurotransmitter systems. I am aware that some of the generalisation from the cellular to the cognitive level in this discussion is goes beyond an acceptable inference from the available evidence. However, this discrepancy may in the future be remedied by the use of ever more specific imaging techniques to map cognitive effects onto brain, and eventually, cellular activity. Moreover, much of the speculation in this thesis concerning neurological changes (especially the chronic effects of ketamine) is based on the animal literature as there is no current work that relates to these mechanisms in humans.

In terms of the cognitive tasks used, as reiterated throughout the thesis, most tap multiple memory and cognitive systems and hence cannot be viewed as diagnostic and independent indices any one 'system'. Indeed, the use of a memory systems framework, whilst useful conceptually, may have obscured some of the common processes operating in these tasks and impaired by ketamine. Ever more careful dissection of the various cognitive components operating within each task will help to shed light on both the common and distinct elements affected by ketamine.

9.6 Methodological Reflections

"Regrets, I've had a few..." Frank Sinatra, My Way

Methodological limitations have been discussed throughout the thesis and only general points will be addressed here. Our investigation of the 'chronic' effects of ketamine in humans was necessarily through the use of a naturalistic sample of drug users. Problems associated with this are: i) ketamine users are poly-drug users ii) possible interactive effects of ketamine with other abused drugs; iii) pre-existing factors that predispose ketamine users to use the drug may mean there are baseline differences from controls regardless of drug use; iv) as a population they score more highly on trait schizotypy (Nunn et al., 2004). In hindsight, it would have been helpful to assess trait schizotypy, especially in ketamine, to use as a covariate in analysing schizophrenia-like effects.

The effects of ketamine, in particular the cognitive effects, are thought to be dependent on plasma levels (Newcomer & Krystal, 2001). As we used a continuous infusion paradigm in our first acute study, plasma levels may have been varying throughout the study which complicates interpretation of the findings. In the second study we sought to address this by using a target controlled infusion but this also yielded higher than expected ketamine levels. In addition, we took only one blood sample in these two studies which did not allow an accurate estimation of the plasma levels at the time of performing each cognitive task. In the pilot study of the MePI the lack of any plasma levels was a limitation. When relating the cognitive effects of ketamine to its

pharmacological action at the NMDA-receptor along with inadequate knowledge of blood levels, a clear problem is the specificity of the drug for this receptor. Ketamine is normally prepared in a racemic mixture of two enantiomers S- and R-ketamine. S-ketamine has greater affinity for the NMDA-R and therefore would have been more appropriate for use in the studies contained in this thesis. However S-ketamine was difficult to obtain for human use in the U.K. at the time of the studies.

The first two acute ketamine studies were between-subjects designs. We used pre and post testing where possible but some tasks were available in only one version (e.g. the Hayling task). Repeated measures design, such as that used in Chapter 9, may be more appropriate in ketamine studies although tachyphylaxis and the interaction of the drug with practice effects on cognitive tasks complicate interpretation of findings in such designs. Practice or carry-over effects across testing sessions may also have been an issue in studies which used an 'acute on chronic' (on drug day 0; off drug day 3) design. However the lack of practice effects in the control groups meant that this was not a problem for the studies in this thesis.

In addition, the use of different measures in some of the chronic and acute ketamine studies limited the comparison across populations. Further, although our relatively crude mapping of schizophrenic symptoms using the SSQ reliably demonstrated changes in the two populations, this does not cover the full range of symptoms. In hindsight, the use of both clinical and observer rated, as well as subjective scales, could have been helpful.

9.7 Implications for future research

For the ketamine 'model' of psychosis, a direct comparison between acute and chronic ketamine and people with schizophrenia on processes such as self monitoring, executive functioning and inhibition would enhance its validity. We are currently collaborating to compare ketamine users directly with first-episode and chronic schizophrenic patients. Further, this thesis has highlighted the utility of comparing the

'chronic' effects of ketamine directly with the acute effects. This approach would be enhanced by giving ketamine in an 'acute on chronic' laboratory setting, to users, poly-drug controls and healthy volunteers where variables such as dose and test setting can be adequately controlled. To give ketamine to users who had reduced their use of the drug would also be interesting, to investigate issues of tolerance and reversibility of impairments, although there may be ethical issues to consider before adopting this approach.

Whilst behavioural studies can provide us with evidence of impairments and clues as to the processes underpinning them, data on the neuroanatomical substrates of these impairments would enhance our undertanding. With regards to ketamine abuse, despite evidence from animal studies of changes in receptor binding and neurotoxicity following repeated ketamine, metabolism in the rat brain is considerably different from that of humans and many of these animal studies used much higher doses than are taken by ketamine users or administered in ketamine studies. PET studies could demonstrate whether NMDA-receptor upregulation has occurred in ketamine users and could shed light on possible DA-ergic abnormalities. In addition, fMRI studies could demonstrate areas of activation on specific tasks following an acute dose of ketamine and in chronic users, as the possibility remains that apparently similar observed behavioural impairments reflect differing underlying neuroanatomical substrates and therefore processes. If activation patterns on acute and chronic ketamine were directly compared with data from patients with schizophrenia on similar tasks, any similarities would be stronger evidence of the construct, not only face, validity of the ketamine model of psychosis.

Directions for future research in relation to specific tasks in this thesis have been suggested in each chapter. In terms of cognition, areas of definite interest are a further characterisation of the effects of ketamine on memory systems and the neuroanatomical substrates of such impairments. Such an investigation has already begun in with working (Honey et al., 2004) and episodic memory (Honey et al., 2005). Of particular interest in terms of findings of this thesis, was the inverse priming observed in the

semantic priming chapter which clearly warrants further investigation. We have a planned collaboration to investigate both the impact of semantic distance on semantic priming and the neuroanatomical substrates, by examining semantic priming during a ketamine infusion using phfMRI and comparing directly with data from the same task in schizophrenics and patients with bipolar disorder.

In this thesis we observed similarities between drug users and the psychosis prone subjects on our novel Me-pulse task. This may be consistent with the notion that similar processes may be impaired in drug abuse and schizophrenia (e.g. Chambers et al., 2001). Theoretically, this stems from the inadequacy of the 'self-medication' hypothesis of schizophrenia (see Goswami et al., 2004 for a review), as many schizophrenics report drug use that exacerbates, rather than alleviates their symptoms. Whilst it was beyond the scope of this thesis to address this point, the novel mepulse inhibition task demonstrated similarities between psychosis prone subjects and drug abusers generally. Our investigation of response inhibition suggested that such deficits in schizophrenia are not glutamatergically mediated. However, the impaired attentional bias to salient environmental reinforcers observed on the Drug Go/No-go task in drug users was somewhat reminiscent of the aberrant salience attribution that has been proposed in schizophrenics (Kapur, 2005). Convergent findings support the view that in schizophrenia frontal cortical activation deficits are related to a disruption in the processing of important environmental information. For example in schizophrenia, processing of novelty has been shown to be impaired on tasks such as the auditory oddball (e.g. van der Stelt et al., 2004). Acute ketamine has also been shown to impair the detection of novelty on such tasks (Krystal et al., 1998a). Further research would help elucidate the interaction between glutamate and dopamine in the assignment of salience to stimuli and may provide a key as to the neurobilogical underpinnings of the increased incidence of drug abuse in schizophrenia.

The longitudinal study reported in this thesis was based upon an opportunistic sample available 3 years after their initial assessment. It would thus be helpful to conduct a longitudinal study of ketamine users and track these participants. This work could also

could examine genetic factors mediating response to ketamine. The Apo-lipoprotein ε allele has been associated with decreased ketamine response in a previous study (Malhotra et al., 1997). Other candidate genes that have been suggested are: neuroreglin, BDNF, NAAG, and genes coding for NMDA-R transcription (Krystal, personal communication).

9.8 The Ph.D. hole ?

"Alice started to her feet for it flashed across her mind that she had never before seen a rabbit with a waistcoat-pocket, or a watch to take out of it, and burning with curiosity, she ran across the field after it, and fortunately it was just in time to see it pop down a large rabbit-hole under the hedge. In another moment down went Alice after it, never once considering how in the world she was to get out again..."

Lewis Carroll, Alice in Wonderland.

A ketamine user in Chapter 5 and one of the healthy volunteers from Chapter 2 both likened the ketamine experience to Alice's Adventures in Wonderland. One feels oneself shrinking and growing, finding oneself in all sorts of curious predicaments and moving rapidly from one bizarre situation to the next. This invokes a further parallel between my own PhD and Wonderland. At times I have felt that I have been following a 'white rabbit', which has led me to investigate a broad range of topics. However, I eventually made it out of the rabbit hole, like Alice, with an (albeit slightly less exciting) story to tell.

Briefly my 'journey' consisted of first, for comparison with chronic effects, an investigation of the acute effects of ketamine on a broad spectrum of cognitive measures. I then focussed on semantic and episodic memory deficits elicited by acute ketamine. I repeated these investigations in ketamine users to allow for comparison between the two populations. I then investigated how enduring these memory impairments were in ketamine users. Given the high incidence of ketamine abuse and drug abuse in schizophrenia, I turned our characterisation of ketamine effects to those that may be theoretically involved in the development and the maintenance of drug

abuse and lastly looked at processes that may underpin symptoms of schizophrenia. Overall, I have provided some of the first evidence of the chronic effects of ketamine in humans and of the ways in which these differ from acute effects. Whilst evidence concerning the effects of ketamine on abuse processes was somewhat inconclusive we have shown differences between drug users and non-drug users and similarities between drug users and psychosis prone individuals. I hope that work will continue to characterise the effects of ketamine both chronically and acutely and investigate neuroanatomical substrates of these effects. Synthesis of the three perspectives I have examined in this body of work (schizophrenia, drug abuse and cognition) was too broad an aim for this thesis but will hopefully occur in the future and these findings may in some way contribute to understanding the common processes within drug use in substance misusers and in people with schizophrenia.

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Appendix

A1

		Mean	Std. Deviation
PRE DRUG			
0-Back RT Hits	placebo	430.16	46.23
	low dose	429.28	48.54
	high dose	445.39	73.82
0-Back RT FAs	placebo	277.50	228.31
	low dose	246.73	196.81
	high dose	218.02	220.63
1-Back RT Hits	placebo	523.45	101.61
	low dose	560.71	92.26
	high dose	559.20	120.20
1-Back RT FAs	placebo	360.81	261.53
	low dose	357.96	284.13
	high dose	351.39	285.52
2-Back RT Hits	placebo	708.69	97.53
	low dose	746.31	106.10
	high dose	707.27	97.25
2-Back RT FAs	placebo	707.61	126.65
	low dose	772.88	138.88
	high dose	764.60	149.06
POST DRUG			
0-Back RT Hits	placebo	436.96	80.44
	low dose	476.19	70.52
	high dose	494.95	83.88
0-Back RT FAs	placebo	114.11	179.12
	low dose	191.49	202.70
	high dose	191.98	217.23
1-Back RT Hits	placebo	486.43	77.39
	low dose	566.05	78.31
	high dose	598.51	95.85
1-Back RT FAs	placebo	385.51	280.47
	low dose	474.09	316.74
	high dose	481.99	283.75
2-Back RT Hits	placebo	639.43	95.02
	low dose	646.41	127.61

	high dose	682.35	90.76
2-Back RT FAs	Placebo	688.61	150.78
	low dose	671.61	148.92
	high dose	675.83	115.50

A2

	DAY 0		DAY 3		DAY x DRUG	DAY	DRUG
	Control	Ketamine	Control	Ketamine			
Dizziness	6.70 (7.48)	41.00 (25.25)	6.45 (7.28)	6.35 (11.66)	***	***	***
Altered time perception	8.10 (7.48)	37.40 (25.91)	7.95 (9.46)	7.85 (15.62)	***	***	**
Impaired concentration	18.80 (15.04)	52.45 (21.09)	14.75 (14.36)	10.35 (14.28)	***	***	**
Altered reality	10.55 (13.32)	43.70 (31.60)	8.25 (11.17)	9.15 (15.10)	***	***	**
Depression	10.70 (12.02)	19.45 (17.90)	7.75 (7.72)	11.00 (14.64)	NS	**	NS
Impaired memory	11.25 (16.60)	37.55 (22.92)	8.70 (11.90)	9.50 (15.66)	***	***	**
Nausea	7.65 (8.44)	19.65 (22.97)	8.85 (9.18)	7.35 (11.63)	**	NS	NS
Visual distortion	8.80 (10.50)	41.75 (26.96)	8.55 (9.32)	8.90 (17.08)	***	***	**
Bodily numbness	4.55 (4.94)	43.30 (28.02)	3.80 (3.94)	8.30 (14.80)	***	***	***
Unsteadiness	8.35 (10.59)	50.85 (22.93)	6.15 (6.88)	9.25 (16.58)	***	***	***
Lack of coordination	10.15 (13.60)	48.55 (29.56)	9.35 (11.31)	8.65 (15.92)	***	***	***
Confusion	9.30 (9.82)	45.10 (26.51)	12.25 (18.72)	8.70 (20.44)	***	***	**
Distortion of sound	2.70 (4.17)	36.80 (23.53)	2.00 (3.32)	10.95 (21.53)	***	***	***
Out-of-body experience	2.55 (3.71)	25.60 (29.09)	3.70 (7.08)	7.85 (13.96)	NS	**	**

***: $p<0.001$, **: $p<0.01$, NS: not significant.

A3

		Mean	Std. Deviation
Pre -drug			
Total hits Phase 1	placebo	74.625	1.024695
	low dose	73.84615	1.863963
	high dose	74.47059	1.007326
Total FAs Phase 1	placebo	4.25	2.620433
	low dose	5.615385	3.594868
	high dose	4.941176	4.249567
Mean RT Hits Phase 1	placebo	407.7836	57.68261
	low dose	410.8465	67.0454
	high dose	423.5361	71.32829
Mean RT FAs Phase 1	placebo	342.1996	63.62561
	low dose	329.0447	52.77205
	high dose	359.7868	82.23169
Total hits Phase 2	placebo	72.1875	2.197536
	low dose	72.30769	1.93152
	high dose	72.94118	1.886484
Total FAs Phase 2	placebo	3.5	2.898275
	low dose	4.384615	4.628507
	high dose	4.470588	3.590224
Total omission reversal errors Phase 2	placebo	0.4375	0.892095
	low dose	0.076923	0.27735
	high dose	0.294118	0.587868
Mean RT Hits Phase 2	placebo	457.5265	57.59075
	low dose	450.4732	68.68204
	high dose	460.5789	65.88883
Mean RT FAs Phase 2	placebo	432.7182	137.652
	low dose	383.7473	71.25484
	high dose	415.2438	113.6545
Post-drug			
Total hits Phase 1	placebo	73.53333	4.155318
	low dose	74.07692	1.705947
	high dose	68.86667	8.943207
Total FAs Phase 1	placebo	5.266667	5.86109

	low dose	6.153846	3.954874
	high dose	6.933333	5.020909
Mean RT Hits Phase 1	placebo	413.2632	45.14384
	low dose	410.6803	48.04025
	high dose	466.7899	125.5596
Mean RT FAs Phase 1	placebo	362.0588	53.99248
	low dose	355.2992	62.39799
	high dose	346.7932	99.67697
Total hits Phase 2	placebo	71.86667	4.103425
	low dose	72.69231	3.400603
	high dose	67	11.66803
Total FAs Phase 2	placebo	5.266667	5.404584
	low dose	5.230769	3.745082
	high dose	8.466667	5.527421
Total omission reversal errors Phase 2	placebo	3.066667	7.095941
	low dose	0.923077	2.21591
	high dose	2.533333	4.405624
Mean RT Hits Phase 2	placebo	443.886	65.69442
	low dose	443.5303	70.4682
	high dose	467.7857	110.6186
Mean RT FAs Phase 2	placebo	378.4821	69.50416
	low dose	365.3784	80.62275
	high dose	365.6	87.55485

A4

D1: KETAMINE	D2: CANNABIS	D3: ALCOHOL
Ketamine	Cannabis	Alcohol
K	Marijuana	Vodka
K-hole	Hashish	Lager
Snort	Weed	Drunk
Line	Stoned	Spirits
Gram	Skunk	Glass
I1: FOOD	I2: SEX	I3: MONEY
Pizza	Orgasm	Cash
Ice-cream	Erotic	Money
Chocolate	Lust	Cheque
Cream cake	Foreplay	Millionaire
Strawberry	Sensual	Gold
Curry	Sexual	Riches
N1: FURNITURE	N2: FABRIC	N3: BUILDINGS
Cabinet	Polyester	Barn
Coffee table	Cotton	Apartment
Armchair	Linen	Office
Hat stand	Nylon	House
Footstool	Corduroy	Bungalow
Bookcase	Tweed	Shed

* Words in blue are ambiguous words related to the drug.

A5

CONFIDENTIAL BODILY SYMPTOMS SCALE . Subject No..... Time.....

Date.....

1. Please rate the way you feel in terms of the dimensions given below
2. Regard the line as representing the full range of each dimension
3. Rate your feelings as they are AT THE MOMENT
4. Mark clearly and perpendicularly across each line

No dizziness	_____	Very severe dizziness
No altered time perception	_____	Very severe altered time perception
No impaired concentration	_____	Very severe impaired concentration
No feelings of altered reality	_____	Very severe feelings of altered reality
No depression	_____	Very severe depression
No impaired memory	_____	Very severe impairment of memory
No nausea or sickness	_____	Very severe nausea or sickness
No visual distortion	_____	Very severe visual distortion
No bodily numbness	_____	Very severe bodily numbness
No unsteadiness	_____	Very severe unsteadiness
No lack of co-ordination	_____	Very severe lack of co-ordination
No mental confusion	_____	Very severe mental confusion
No distortion of sound	_____	Very severe distortion of sound
No 'out of body' experiences	_____	Very severe 'out of body' experiences